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CALLING ATTENTION TO 387

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SOME PHYSIOLOGICAL ASPECTS OF ADOLESCENCE

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The increase in growth rate followed by the attainment of sexual maturity has long been regarded as the chief characteristic of adolescence. However, the physiological mechanisms upon which these changes are based have received scant attention. Other than basal metabolism and the inception of menarche in girls, few studies of the physiological aspects of adolescence have been made in humans. In recent years, repeated measurements on the same children during growth have demonstrated the individuality of the growth process and the serious limitations of the average values usually regarded as "age-norms" (Shuttleworth, 1938) obtained from averages of different children measured at successive ages. Recognition of such individual differences in rates of growth and maturation is essential to the proper interpretation of average curves which continue to serve as the background. The aim of the present report is to present the results of a study made of some physiological changes taking place in average children at adolescence.

To those who practice medicine among adolescents it should be made clear that such studies can offer no specific recommendations of when medical intervention is desirable or what specific procedures or techniques should be applied. Questions of *what* to do can be answered only by specialists in the practice of medicine. Questions of *when* to do it must be left to the individual judgment of the clinician. However, knowledge of studies of average individuals plays an important part in such clinical judgments. Increased knowledge of average developmental processes will certainly do much to increase the probability that the judgment of the clinician will be to the best interests of the patient. Hence, no apologies need

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[1]The experimental work reported here was carried out by Dr. Shock while Assistant Professor of Physiology and Research Associate, Institute of Child Welfare, University of California, Berkeley, California. Presented at The University of Texas Medical Branch, Galveston, February 10, 1946.

be offered for the following presentation of some of the physiological changes in average adolescents.

The University of California Study of Adolescence

The University of California study of adolescence was planned to study the individual characteristics of adolescent development (Jones, 1939). In this study measurements were made on the same children at 6 or 12 month intervals over the age span of 11.5–18 years. The testing program included anthropometric measurements, medical examinations, psychological testing, educational tests, personality questionnaires and tests, motor tests for strength and skill as well as physiological measurements, such as pulse rate, respiration rate and volume, blood pressure, basal metabolism, metabolic and cardiovascular response to exercise, etc. For the physiological measurements, 50 girls and 50 boys were chosen from five elementary schools of Oakland, California, on the basis of the willingness of their parents to coöperate in a long term study and the probability of permanent residence in the community. No characteristic of the child was used in the selection of subjects. When first tested the children had a mean age of 11.87 years (S.D.=0.5 year). Tests were repeated at six-month intervals.

On the morning of the physiological tests, the child was brought by automobile to the laboratory, without breakfast. After height and weight were measured, a standard 12.5 cm. sphygmomanometer cuff with leather backing was attached to the left arm. After determinations of blood pressure (by the auscultatory method) and pulse rate were made with the subject standing, he lay down on a cot for 20 minutes while three additional measurements of pulse rate and blood pressure were made. A Siebe-Gorman half-mask was then tied securely over the nose and mouth of the subject, and after testing for leaks, three eight-minute tests of basal oxygen consumption were made by the Tissot open circuit method. Additional determinations of blood pressure and pulse rate were made at the end of each eight-minute metabolism period. After the metabolism tests, alveolar air samples were collected by the Henderson-Morriss technique.

The subject then climbed five flights of stairs, (to a height of 58.5 feet) as rapidly as possible, after which he lay down on a cot. Continuous collections of expired air were begun immediately and continued for a period of 45–60 minutes. Determinations of pulse rate, blood pressure and respiratory rate were also made at frequent intervals during the recovery period.

The data obtained after this exercise have not been reported but are presented in part and discussed in another paper (see p. 368 this issue).

The basal measurements were repeated according to the same schedule on the following morning.

Age Changes in Cardiovascular Measurements Under Basal Conditions

Average curves, based on chronological age groups, were prepared for all measurements taken. In Figure 1 the average

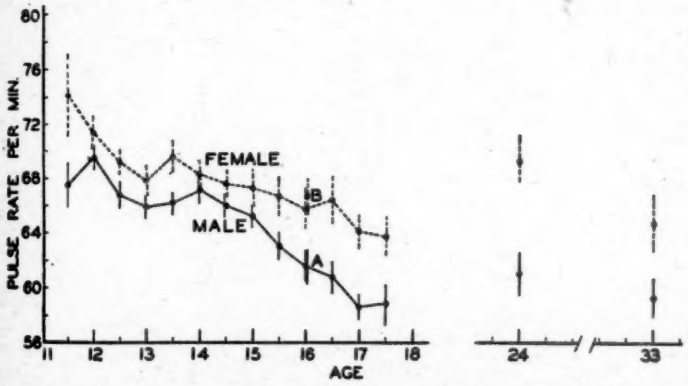

Figure 1. Average basal pulse rates of boys and girls. Connected points were obtained from measurements of the same children as they matured. Points shown at ages 24 and 33 years obtained from tests of other subjects. Points marked A and B are average values for 50 additional boys and 50 additional girls, aged 15.5–16.5 years who were tested for the first time at this age. The length of the vertical line through each point indicates ± 1 standard deviation of the mean.

O————O Males; O— — —O Females

This explanation applies to all other figures shown. (From Am. Jour. Dis. Child., 68:18, 1944.)

basal pulse rates for girls and boys are shown (Shock, 1944). In this figure the vertical lines through each experimental point indicate ± 1 standard error of the mean. These curves show an average decrease of 8–9 beats per minute for boys and girls during adolescence. The average rate for girls is from two to six beats per minute faster than for boys of the same age. This sex difference in pulse rate increases somewhat with age. The slight rise in pulse rate observed in girls between the ages of 13.0 and 13.5 years is not statistically significant when averages are calculated on the basis of chronological age, but when girls are grouped on the basis of physiological maturity (as estimated from the age at first menstruation) evidence of a rise in pulse rate just prior to menarche is obtained (See Figure 15).

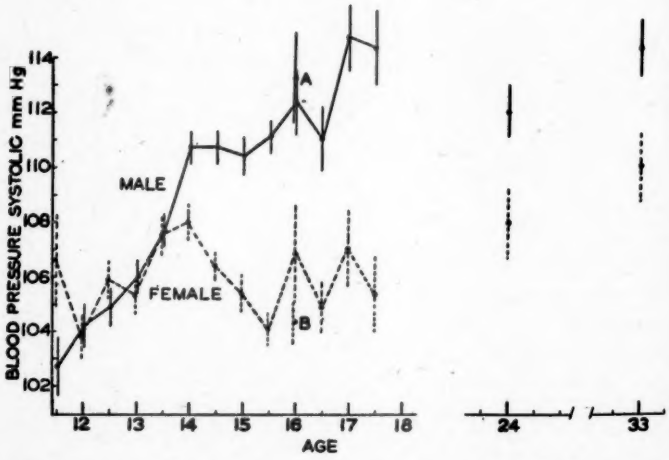

Figure 2. Curves for average systolic blood pressure under basal conditions. O————O Males; O— — —O Females. (From Am. Jour. Dis. Child., 68:18, 1944.)

Figure 2 shows the average systolic blood pressure for adolescent boys and girls (Shock, 1944). Between the ages of 11½ and 13½ years the average blood pressure rises from 103 to 108 mm. Hg in both sexes. After the age of 13½ the systolic pressure of boys continues to rise, reaching a value

of 114 mm. at the age of 17½, while that of girls drops slightly, reaching a minimum of 104 mm. at the age of 15½. Beyond this age there is a slight rise in pressure in girls reaching 106 mm. at 17½ years. Thus a sex difference in blood pressure develops during adolescence which persists throughout life.

Changes in the diastolic blood pressure with age are shown in Figure 3. Between the ages of 12 and 14½ diastolic pres-

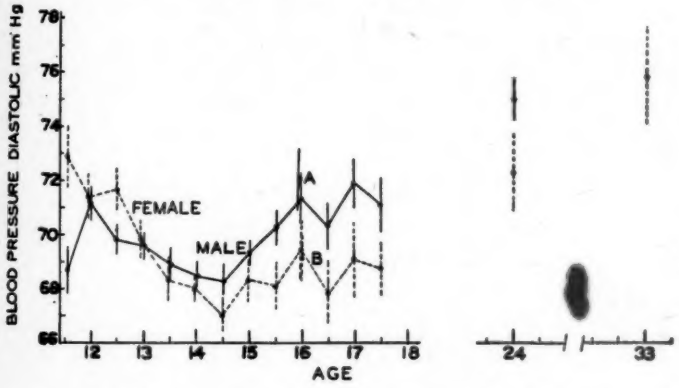

Figure 3. Curves for average diastolic blood pressure under basal conditions. O————O Males; O— — —O Females. From Am. Jour. Dis. Child., 68:18, 1944.)

sures of both boys and girls tend to diminish, reaching a minimum of 67–68 mm. at 14½ years. After this age, the average pressure rises again so that at 17½ years the values are practically the same as they were at 12 years. This gradual rise in diastolic pressure continues throughout life. The difference between girls and boys is not statistically significant at any age.

Figure 4 shows the development of a sex difference in pulse pressure in adolescent children (Shock, 1944). The average pulse pressure rises from 34 mm. at age 11½ to 39 mm. at age 13½ in both sexes. Beyond this age the pulse pressure of boys continues to rise while that of girls falls, resulting in a significant sex difference between the ages of 15 and 17½ years. This sex difference disappears in adults.

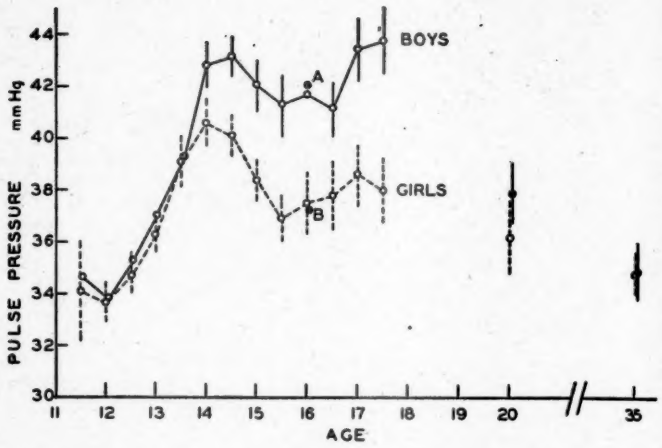

Figure 4. Curves for average pulse pressure under basal conditions. O———O Males; O— — —O Females. (From Am. Jour. Dis. Child., 68:19, 1944.)

Age Changes in Respiratory Measurements Under Basal Conditions

Samples of alveolar air collected at the end of expiration with the sampling valve described by Henderson and Morriss (1917) were analyzed for CO_2 content in a 10 cc. Haldane apparatus. The probable error of determinations of CO_2 tension made on successive days varied from 0.9 to 1.8 mm. Hg (Shock, 1941). Average curves, presented in Figure 5 show a statistically significant rise in alveolar CO_2 tension in boys from 40.5 mm. Hg at 11.5 years to 44.7 mm. Hg at 17.5 years. In girls no significant change in alveolar CO_2 tension was observed with age, although the sex difference became statistically significant at the age of 13 years.

During adolescence the average basal respiratory rate diminished from 16½ per minute at 11½ years to 14½ per minute at 17½ years (Shock and Soley, 1939). No significant difference between girls and boys was observed. However, all measurements of respiratory volume show a definite sex difference. When no correction for differences in body size

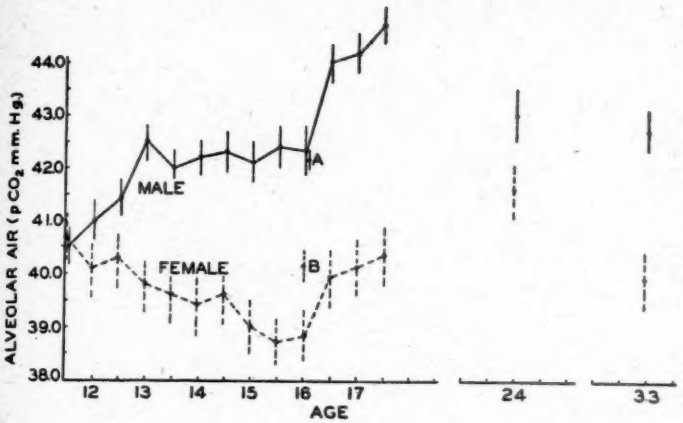

Figure 5. Age changes in average CO_2 tension of alveolar air.
O————O Males; O— — —O Females.

is made, differences in basal respiratory volume of boys and girls are quite marked, as shown in Figure 6. In boys the

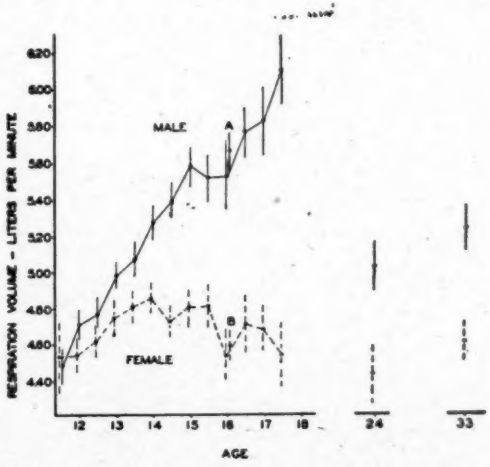

Figure 6. Age changes in average respiratory volume under basal conditions. Liters per min. reduced to standard conditions.
O————O Males; O— — —O Females.

basal respiratory volume increases from 4.50 l./min. at age 11½ to 6.0 l./min. at age 17½, while in girls, little change with age is observed. When respiratory volumes are corrected for differences in body size by dividing by the surface area, the values for both boys and girls diminish with increasing age and the sex difference of about 400 cc. per sq. m. per minute remains uniform throughout adolescence (See Figure 7). Both boys and girls have about the same tidal volumes

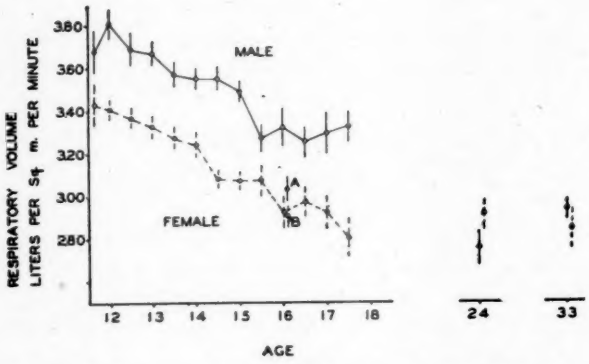

Figure 7. Age changes in average basal respiratory volume corrected for body size. Liters per square meter of body surface per minute. O———O Males; O— — —O Females.

before the age of 14, but thereafter a marked sex difference appears (Figure 8). Values for girls remain at 300–350 cc. per breath, while those for boys increase to 400 cc. per breath. The physiological dead space[2] is significantly greater for boys than girls as shown in Figure 9. This difference which develops during adolescence is maintained in adults. Thus, it is apparent that the respiratory differences between males and females have their origin during adolescence.

[2]The physiological dead space of the respiratory passages represents that volume of air which does not reach the alveoli during respiration. It may be calculated from the formula

$$\text{Dead space} = \text{tidal volume} - \text{tital vol.} \times \frac{CO_2 \text{ content expired air}}{CO_2 \text{ content alveolar air}}$$

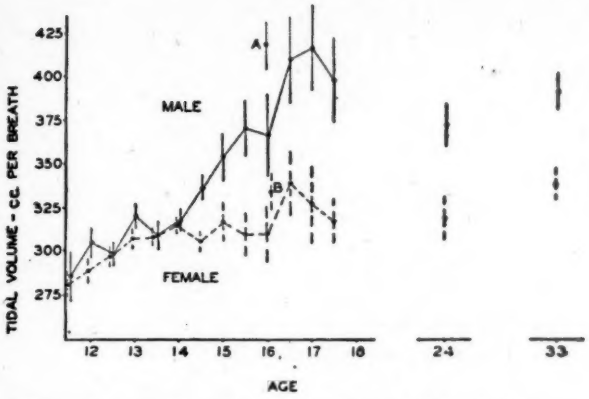

Figure 8. Age changes in average tidal respiratory volume under basal conditions, cc. per breath.
O———O Males; O— — —O Females.

Age Changes in Basal Metabolism

From the correlations between the average of three determinations of basal metabolism on two successive days the probable error of estimate was computed. The error of estimate of

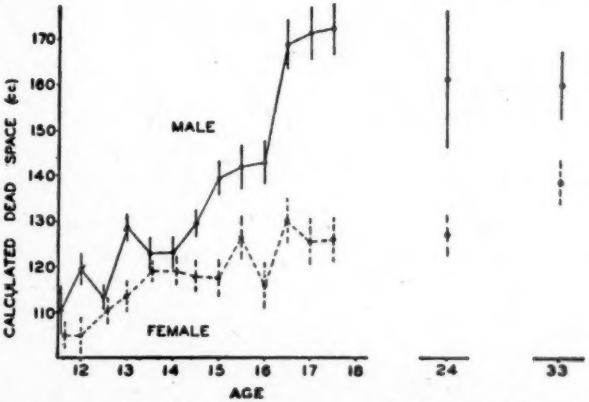

Figure 9. Age changes in the average physiological dead space of the respiratory system, in cc.
O———O Males; O— — —O Females.

basal metabolism determinations carried out under the conditions of our experiments varied between 1.26 and 1.99 cal. per sq. m. per hr. for both boys and girls between the ages of 11.5 and 17.5 years (Shock, 1942) (equivalent to 3–5 per cent deviation). Since no systematic change in reliability of measurement was found with increasing age in children subjected to repeated tests and since the probable errors of estimate for groups of children tested only once were no greater than for children of the same age who had been tested ten times previously, it may be concluded that the reliability of metabolism measurements is not significantly altered by repeated testing, provided a preliminary training test is given.[3]

From the average of the six determinations of basal metabolism made on two successive days, average values were calculated for each half-year age interval. Figure 10 shows the

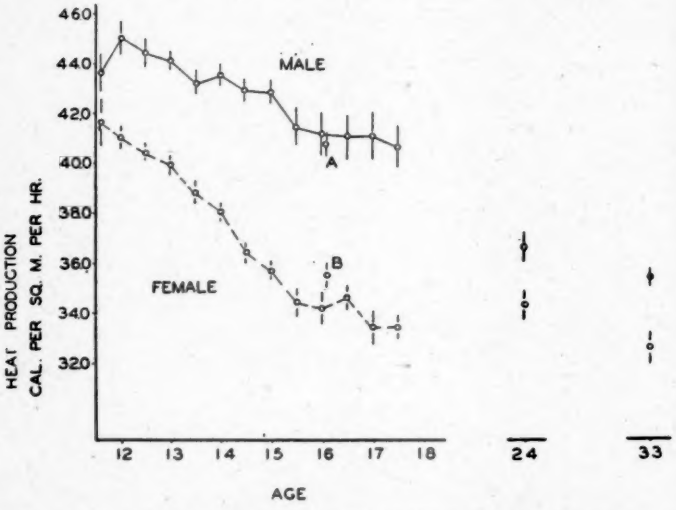

Figure 10. Age changes in average basal heat production. Calories per square meter of body surface per hour.
O————O Males; O— — —O Females.
(From Am. Jour. Dis. Child., 64:23, 1942.)

[3]All subjects were given an introductory training test in which they were familiarized with the application of the face mask and the entire procedure of the tests. No analyses were made for the training test.

average basal heat production for males and females. The points marked A and B in this chart are average values for 50 additional boys and 50 additional girls aged 16 years who were tested for the first time at this age. The vertical lines through each point indicate the limits of ± 1 standard deviation of the mean values. The connected points were obtained from repeated examinations of the same children. Points shown at ages 24 and 33 years were obtained from tests made on different subjects under comparable conditions. Since the measurements made on the control groups of 16 year-old subjects (Groups A and B of Figure 10) do not differ significantly from measurements made on the children subjected to repeated testing, there is no reason to believe that the results obtained in the cumulative study have been significantly altered because of the extensive training or laboratory experience of these subjects.

These data show that the average basal metabolism decreases gradually throughout the adolescent period. In girls, the rate of fall of basal metabolism has become very small by the age 16–17 years. In boys, however, the basal metabolism continues to decrease beyond the age of 18 years, thus offering additional evidence of earlier maturity in girls than boys.

Due to the wide-spread use of the Boothby-Sandiford norms of basal metabolism (Boothby and Sandiford, 1929), the results of this study were calculated in terms of per cent deviation from these norms. Figure 11 shows the average per cent deviation from these norms at each age level. The basal metabolism of Oakland boys averaged 6 per cent lower than that for Minnesota boys during adolescence. The average values for Oakland girls are 5 per cent lower than those for Minnesota girls at 11.5 years, but by the age of 15.5 years the average deviation from Minnesota girls has increased to 12 per cent. It is important to realize that the range of values for basal metabolism which will include 95 per cent of a normal population at any given age (between 11.5 and 17.5 years) is greater than the average change in metabolism with growth over the adolescent period. Figures 10 and 11 also show that the conventional limit of ± 10 per cent deviation from the mean value for normality is too narrow for this age span and should be

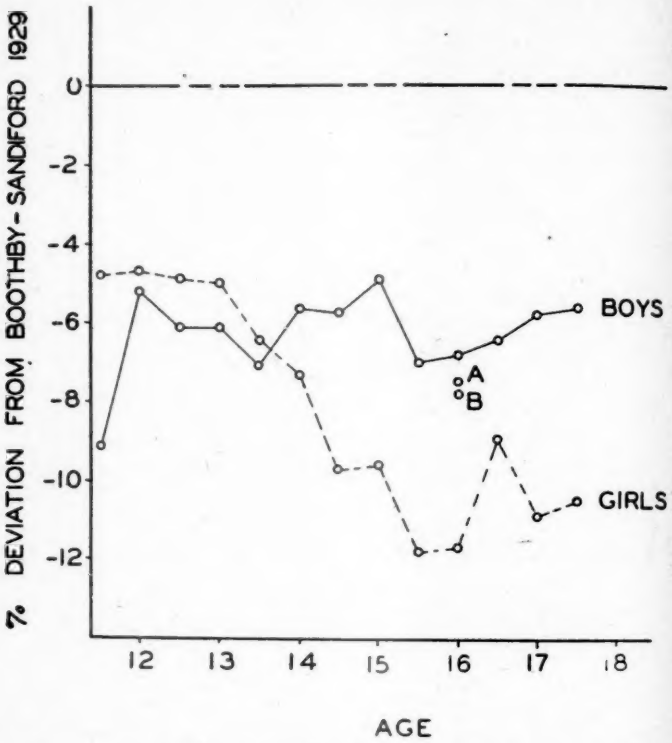

Figure 11. Age changes in basal metabolism. Average per cent deviation from Boothby-Sandiford norms.
O———O Males; O— — —O Females.
(From Am. Jour. Dis. Child., 64:30, 1942.)

extended to at least ± 15 per cent if norms expressed in terms of chronological age are to be used. This wide range of normal values in adolescence emphasizes the need for additional information on the state of sexual maturity, rate of growth and other factors for accurate characterization of the metabolic status of the individual child. Such information may often be obtained from an examination of individual growth curves of metabolic rate.

While the curves shown in Figure 10 demonstrate that a gradual fall in basal metabolic rate is characteristic of the

adolescent period, they provide no basis for predicting the pattern of age changes in individual boys and girls (Shock, 1944). In fact, only ten out of one hundred cases studied exhibited the uniform, even, decrease characteristic of the average curves. Over half of the subjects showed periods of very rapid change as illustrated in Figures 12 and 13. Be-

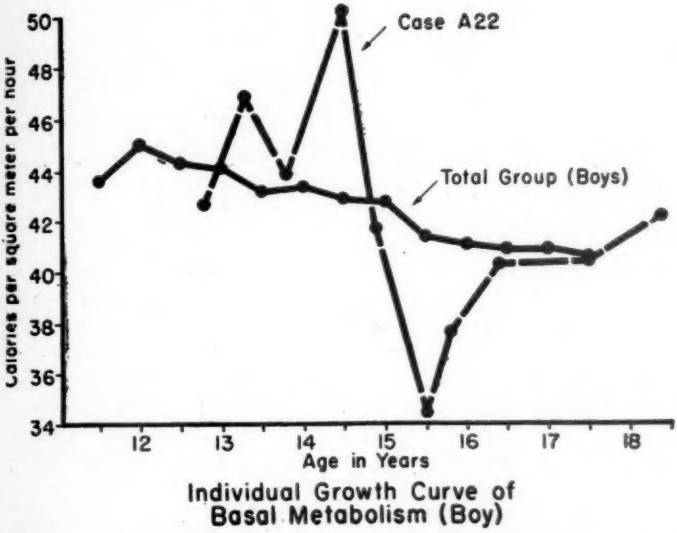

Figure 12. Individual growth curve of basal metabolism of a boy compared with the average curve. ●—— ——● Cace A22; ●————● Mean of group (boys). (From 43rd Yrbk., Nat. Soc. Study Educ., Part I, 43:63, 1944.)

cause these periods of rapid change occur at different chronological ages in different subjects, distinctive individual patterns are lost in the averaging process. A few subjects revealed an age trend opposite to that of the average, that is an increase in basal metabolic rate with age. These subjects, five in number, tended to be small, slow-maturing and physiologically unstable as shown by poor agreement between measurements of metabolism made on successive days.

Similar discrepancies between individual and average growth curves have been found for other physiological variables as

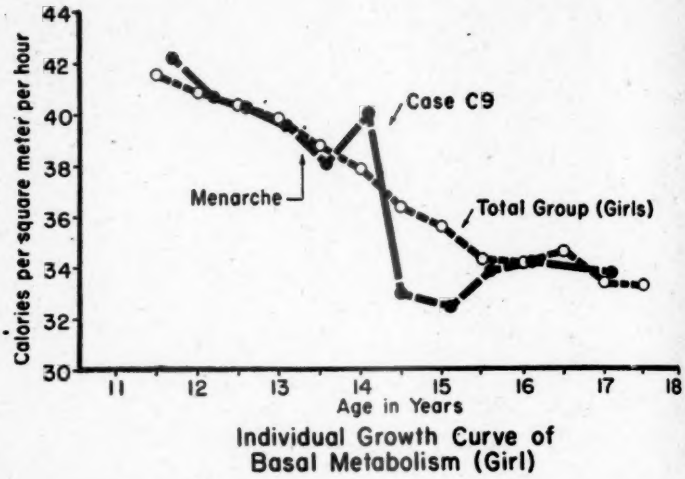

Figure 13. Individual growth curve of basal metabolism of a girl compared with the average curve. ●— — — —● Case C9; O———O Mean of group (girls). The arrow indicates the age at which first menstruation occurred in this girl. (From 43rd Yrbk., Nat. Soc. Study Educ., Part I, 43:63, 1944.)

well. Hence it is important to bear in mind that wide individual differences in patterns and rate of physiological development occur among so-called "normal" children and that children of the same chronological age may be quite unlike in their degree of physiological maturity.

Age Changes in Hormone Excretion

In view of the role of endocrine secretions in stimulating sexual development and maturity, information about the amount of such hormones present in the blood is of utmost importance. At the present time we do not have analytical methods of sufficient specificity and sensitivity to determine quantitative variations in the amounts of gonadotrophic, estrogenic or androgenic hormones present in the blood stream. Hence, attention has been directed to determining the amounts of these substances excreted in the urine. The methods used often depend on the biological response of immature test animals (rats, mice, chicks) to the injection of extracts prepared

from urine samples. For such tests the total urine output must be collected over a period of several days in order to yield enough of the hormones to permit adequate bioassays. Furthermore, the meaning of increased urinary excretion of a hormone is difficult to assess. An increased excretion is usually taken as an indication of increased production of the hormone by the appropriate gland. There is no definite assurance, however, that the increased excretion is not the result of diminished utilization, since the hormone appearing in the urine represents the amount that is wasted or lost to the animal body. Since laboratory facilities were unavailable for hormone assays in the California study, no observations were obtained on the children under consideration. However, data from other studies will be briefly viewed.

There is no general agreement on the amount of gonadotrophic hormone excreted by different aged children. In perhaps the most adequate research reported, Greulich *et al.* (1942) analyzed urine specimens of 64 boys aged 10–17 years. At ages less than 12½ years all tests were negative for gonadotrophic hormones; at ages greater than 12½ years some tests

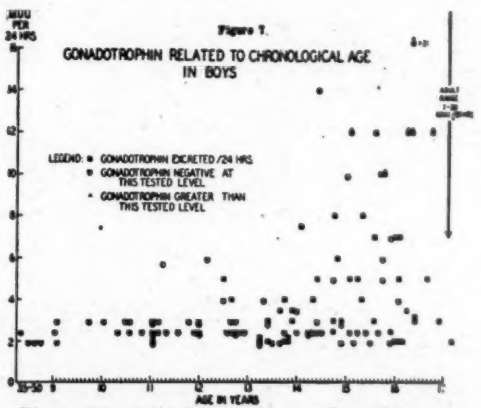
Figure 7.
GONADOTROPHIN RELATED TO CHRONOLOGICAL AGE
IN BOYS
MUU PER 24 HRS
LEGEND: ■ GONADOTROPHIN EXCRETED /24 HRS.
O GONADOTROPHIN NEGATIVE AT THIS TESTED LEVEL.
^ GONADOTROPHIN GREATER THAN THIS TESTED LEVEL
AGE IN YEARS

Figure 14. Age changes in gonadotrophin excretion in boys. ■ Gonadotrophin excreted in mouse units per 24 hours. $\overline{O}$ Gonadotrophin negative at this tested level. ^ Gonadotrophin greater than this tested level. (Greulich, *et al.*, Monographs of the Society for Research in Child Development, 7:54, 1942.)

were positive, while at ages greater than 16 years all tests were positive. As would be expected, the boys were more homogeneous with respect to hormone excretion when classified into maturity groups than when classified on the basis of chronological age. These results are shown in Figures 14 and 15.

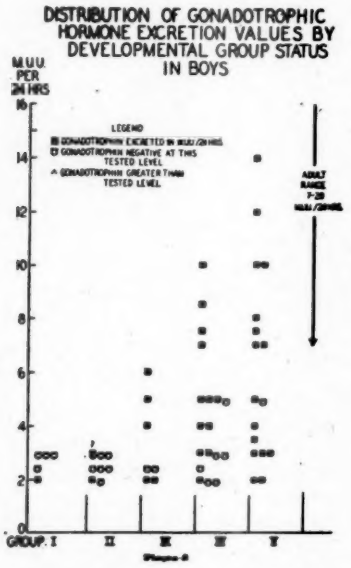

Figure 15. Excretion of gonadotrophin in the urine of boys arranged by developmental status. ■ Gonadotrophin excreted in mouse units per 24 hours. Ō Gonadotrophin negative at this tested level. ⩚ Gonadotrophin greater than this tested level. (Greulich, *et al.*, Monographs of the Society for Research in Child Development, 7:55, 1942.)

Both boys and girls excrete small amounts of estrogenic hormone. Before the age of 10 years the amount excreted is from 3 to 20 international units per 24 hours for each sex. After the age of 11 the daily excretion of estrogens increases rapidly in females, reaching values of 200–400 I. U. per 24

hours, while that of males increases only slightly. (See Figure 16.)

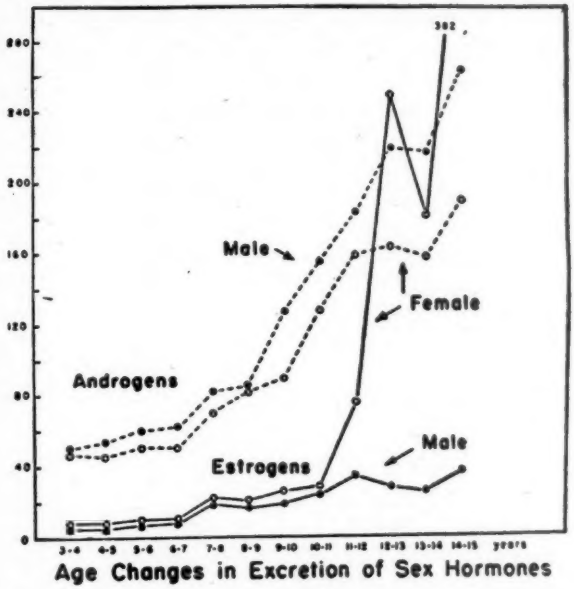

Figure 16. Age changes in excretion of androgens and estrogens in the urine of boys and girls. Estrogen assays are expressed in international units. Colorimetric analyses for total 17-ketosteroids, expressed in arbitrary color units were used as the index of androgens excretion. Average values. (From the 43rd Yearbook, Nat. Soc. Study Educ., Part I, 43:75, 1944.)

Greulich *et al.* (1942) using the comb growth response in day-old chicks, determined the daily excretion of male sex hormone in 82 boys between the ages of 8 and 17 years. The average daily excretion increased from 8.5 I. U. per 24 hours at age 8–14 to 10.8, 21.5 and 24.8 for 14, 15, and 16 year old boys respectively. The range of values, however, was very great: from 1–34 I. U. among 8–14 year old boys and from 2–57 I. U. per 24 hours among the older boys.

From these results we may tentatively conclude that before the age of 11 or 12 years both boys and girls excrete measurable amounts of both male and female sex hormones. Slightly

greater amounts of male hormone are excreted by boys than girls and slightly greater amounts of female sex hormones are excreted by girls than boys, but the differences are not striking. After the age of 11 years, the excretion of female sex hormone markedly increases in girls and the excretion of male hormone increases correspondingly in boys so that a large difference between the excretory patterns of the two sexes becomes established.

Effects of Sexual Maturation on Other Physiological Functions

The effect of sexual maturation on other physiological functions was investigated in the following manner (Shock, 1943). For each girl the time (or age) at which the physiological tests were made was expressed as months before or after menarche instead of as chronological age. Mean values of blood pressure, pulse rate and basal heat production were computed for each six month interval before or after menarche. If at menarche there were a sudden change in physiological

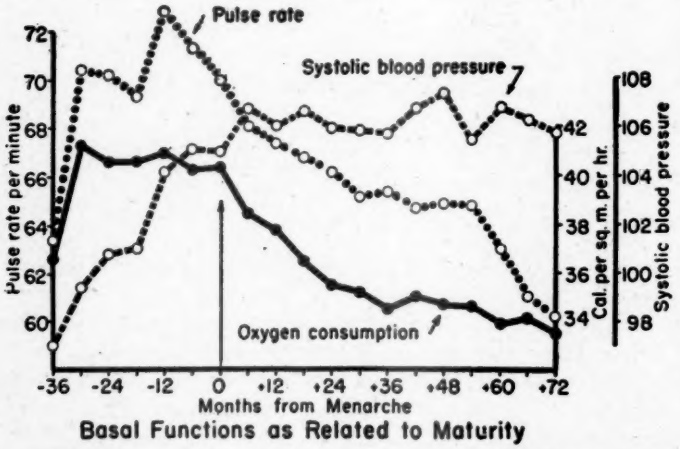

Figure 17. Basal functions as related to sexual maturity in girls. Average values based on age deviation from menarche of the individual case. The vertical line at O indicates the beginning of menstruation. O • • • • • O Pulse rate; O — — — — O Systolic blood pressure; ●————● Basal oxygen consumption. (From the 43rd Yearbook, Nat. Soc. Study Educ., Part I, 43:75, 1944.)

conditions within the body which produced changes in blood pressure, for instance, the average curve plotted in the manner outlined above would show a sudden change in slope or direction of trend at the time of menarche. The results of this analysis for 52 girls are shown in Figure 17. From this figure it may be seen that the progressive rise in systolic blood pressure characteristic of childhood ceases at menarche and thereafter maintains a uniform level. Pulse rate also rises during the premenarcheal years attaining a maximum value in the year preceding menarche. After menarche pulse rates decline. Perhaps the most striking non-sexual physiological change at menarche is the sudden fall in basal metabolism which commonly follows the beginning of menstruation. Thus the decrease in basal metabolism which characterizes the adolescent period actually takes place rather rapidly over the 2–3 years following menarche.

Discussion and Summary

Some of the results obtained from repeated measurements of girls and boys taken during adolescence have been summarized in terms of average curves. This analysis has shown that some but not all differences between the sexes with respect to physiological measurements arise during adolescence. For instance the lower basal oxygen consumption of females is present before adolescence. On the other hand differences in blood pressure, respiratory volume, etc., first appear during the adolescent period. Examination of average curves gives the impression that the physiological changes taking place during adolescence are slow and gradual. However, when individual growth curves for certain physiological measurements are plotted, it is quite apparent that in many adolescents the physiological adjustments of this period are rapid and abrupt, and that wide variations above or below the average curves may be present in different individuals at different times. This information is of considerable value in interpreting the results of physiological measurements in individual cases. The increased variability in physiological measurements during adolescence may be taken as an indication that one of the important aspects of development is learning to maintain

physiological equilibrium (Shock, 1944). In adults, less variability in physiological measurements is encountered because the organism has learned to utilize all its available adaptive mechanisms in the maintenance of homeostasis. In the adolescent these processes are still being organized and synthesized. Thus it may be helpful to regard adolescence as a period of physiological learning. An example of such physiological learning is the regulation of menstrual periodicity. When menstruation first begins in adolescent girls it does not usually recur at uniform intervals. However, over a period of several years the physiological factors involved in menstruation become better coördinated and a greater regularity of interval is established (Bayer, 1940). The individual organism has learned to maintain the even homeostatic adjustment of the adult upon which certain physiological rhythms, such as that of menstruation, may be superimposed. As a result of such learning, physiological fluctuation is reduced and the uniformity of the adult state is attained.

To those concerned with the direction and guidance of adolescents this period of development often seems burdened with a multitude of problems. Most of these problems are associated with the adjustments which the adolescent is called upon to make to an environment dominated by adults at a time when his own internal environment is in a state of flux. The unpredictable variations in the adolescent's behavior, so exasperating to adults, may often have a physiological basis. One example is the stirring of sexual instincts, resulting from the increased production of sex hormones within the adolescent's own body. The typical adolescent behavior which results is often at odds with standards set by adults. Similarly the listlessness and apathy encountered in some adolescents may be reflected in periods of lowered metabolism. Until the adolescent can reconcile his own internal environment with his social and cultural environment, some degree of conflict and psychological turmoil will likely prevail.

Another source of psychological tension and anxiety to adolescents is the great difference in rate at which different individuals approach maturity. When Jimmy's pal, Johnny, suddenly surpasses him in height and begins to shave, Jimmy

may wonder whether he himself is "normal." As the discrepancies between his appearance and that of his associate become more prominent, he becomes increasingly anxious about his developmental status. It is not surprising that, in order to prove himself, he sometimes resorts to behavior which is far from socially acceptable to adults (Jones, 1943; Stoltz and Stoltz, 1944). On the other hand the rapidly maturing adolescent may find himself in hot water because adults expect from him behavior or performance consistent with his size. Since size and social or intellectual maturity do not necessarily proceed together, it often happens that the "large" adolescent is relatively immature. Thus he may be unable to meet the expectations of adults with respect to performance or behavior. The failure to "deliver" in the eyes of his peers or of adults is a not uncommon source of psychological tension. It is quite probable that in many an adolescent the inadequacy which he feels or observes has a definite physical or physiological basis, but the nature of the originating or contributing factors may vary widely among different individuals. Knowledge of individual differences in rates of maturing, as illustrated by the observations here reported can do much to minimize the emphasis placed, all too often, by school physicians and counselors, on attaining "normal" values. The pediatrician is in a strategic position to aid developing adolescents in understanding and evaluating their own development.

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THE THYMUS GLAND

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No structure of the body is less understood, nor, with few exceptions, has had more functions attributed to it, than the thymus gland. Unlike the development of knowledge regarding most organs and problems, there has been no definite trend of thought regarding the thymus gland, nor have any salient discoveries been made to indicate the function of the thymus, or for that matter, the constitution of the gland. For instance, embryologically it is common knowledge that the thymus, together with the parathyroids, arises from the third, and sometimes the fourth, branchial pouch, the thymus from the ventral, the parathyroids from the dorsal diverticulum, and normally descends to its position just beneath the upper part of the sternum. Here, definite knowledge of the thymus gland ends and in the literature one finds from this point a gradual progression of confusing details regarding the anatomy and function of the organ.

Anatomy: The thymus has three distinct tissues: a medulla which contains the Hassall's corpuscles, a cortex which is principally a lymphoid structure containing small, round lymphocytic cells, and the supporting connective tissue. There are marked differences in the proportions of these constituent parts at different age periods. The significance of the decrease in size of the total gland and especially of its parenchymal tissue with increasing age is a subject of considerable controversy.

The size or weight of the thymus at different ages has been the source of much confusion, brought about to a great extent by the fact that many of the older studies were based upon observations of pathologic subjects. Recent work has abundantly demonstrated that the size of the organ is dependent upon the general nutritional state of the body. Thymus tissue is extremely sensitive to the general nutritional status of the

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body. According to Boyd, inanition of any cause, deprivation or disease, will reduce the weight of the thymus by one-third within a period of three days. The marked range in weight of the normal thymus is indicated in the following table (from Mitchell and Nielson):

Wt. of Normal Thymus Gland (Grams)

	Average	Range
Birth	10	3–31
2 months	20	4–31
6 to 11 yrs.	30	13–55
20 yrs.	20	7–50
Old age	10	3–30

While the thymus increases in size until about the age of puberty, it should be noted that in relation to total body weight it decreases from the time of birth; slowly in the first year, more rapidly throughout childhood, and even somewhat more rapidly after puberty. Boyd has shown also that in normal thymus glands only the medulla begins to involute at about the age of puberty—involution of the lymphoid tissue in the cortex having started at four years of age—while the connective tissue continues to increase until old age.

Functions and Physiology: The function or functions of the thymus have never been satisfactorily established. While it is generally agreed that the thymus serves a lymphopoietic function, there is no agreement on the many other functions which have at one time or another been attributed to it. Among properties which have at one time or another been assigned to the thymus are that it influences the development of the bones; that it is a factor in the cause of exophthalmic goiter; that it affects the coagulability of the blood; that it regulates blood pressure; that it has an effect on calcium and phosphorus metabolism; that it exerts some action upon the development of the genital system and influences general body growth; that it is concerned in the production of certain forms of anemia and of the primary myopathies; that it acts as a blood forming organ; and that it produces a toxin which may be the cause of sudden death.

Experimental work on the functions of the thymus is massive. Only a few of the results and conclusions will be quoted.

A hormone from the thymus has not been conclusively demonstrated. The effect of thymectomy on the sex glands and suprarenals is still disputed. Highly contradictory results are reported from experimental studies on the influence of the thymus on growth. Park and McClure were unable to demonstrate any significant changes in puppies from which the thymus glands were removed and concluded that in this animal the organ is not essential to life and serves no essential need. Einhorn and Rowntree claim that there is a retardation of growth in the offspring of thymectomized rats. Furthermore, their results following the repeated intraperitoneal injection of thymus extract into successive generations of rats have led them to conclude that the fertility of the parent rats was increased and that the growth and development of the offspring of the treated rats showed cumulative acceleration in successive generations. These striking results have not been confirmed, though numerous attempts have been made to duplicate them.

A possible interrelationship between the thymus and the generally recognized endocrine glands is accepted by many as the strongest evidence that the thymus may have an endocrine function. There is an amazing amount of material in this respect which is difficult to evaluate. Some of the principal reported relationships are: thymectomy results in genital hypoplasia, enlargement of the adrenal cortex, compensatory hypertrophy of the thyroid, and retardation of growth in the successive generation. Thymic involution may be prevented or delayed by castration, adrenalectomy, thyroidectomy or hypophysectomy in the prepuberal stage.

The above illustrates the existing confusion. Much further investigation is needed before the functions and the physiology of the thymus gland can be put on a firm basis. At the present time there is no knowledge of the function of the thymus that is useful clinically in the management of the indefinite syndromes which have been attributed to dysfunction of the thymus in humans.

Pathology: Only brief consideration need be given to pathology. Nutritional atrophy is by far the most frequent disease

of the thymus. This gland, like all lymphatic structures, involutes rapidly during inanition. In nutritional atrophy, as in physiological atrophy following puberty, the cortex is reduced more than other portions, primarily because of the migration of lymphocytes. Enlargement usually consists of simply hyperplasia in which the medulla and cortex of the organ share equally. Edema of the gland is found not infrequently and also hemorrhage, either petechial or larger in size. There may exceptionally be found an inflammatory process—a thymitis. Metastatic abscesses may occur during bacteremia. The breaking down of cells due to syphilis seems to account for the so-called Dubois's abscesses. Tuberculosis of the thymus is rare as a primary manifestation, if it occurs at all, although there may be secondary involvement from tuberculosis elsewhere in the body.

Neoplastic disease of the thymus, either primary or metastatic, is not common. There have been described lipoma, fibroma, cysts of various sorts, lyphangioma, carcinoma and sarcoma. When large, these tumors may produce the same clinical picture as other large mediastinal tumors.

Recent interest has been centered in the relationship of the thymus to the pathogenesis of myasthenia gravis. Bell, in reviewing the reports of all cases of myasthenia gravis since 1901, found that the thymus was definitely abnormal in 49%. The significance of thymic hyperplasia and thymomata in myasthenia gravis is not known, but the frequency of their occurrence and the good results following extirpation and irradiation suggest some relationship.

Symptoms: The symptoms attributed to the thymus may be generally divided into two groups: respiratory obstruction and sudden death.

The Thymus and Respiratory Obstruction: For more than 100 years the role of the thymus in respiratory obstruction has been debated in medical literature. Whether the thymus is ever responsible for obstruction of respiration of any significant degree is a controversial point. Thymic stridor is an indefinite term which has come to include a wide variety of

obstructive manifestations such as coughing, choking, crowing, dysphagia, sudden pallor, convulsions and the combination of dyspnea and cyanosis.

Can the thymus actually compress the trachea? The most direct evidence would be visual demonstration during life. Jackson has claimed by means of the bronchoscope to have seen tracheal compression by the thymus in over three hundred patients who had obstructive symptoms. Pancoast and others have apparently demonstrated roentgenologically that the thymus actually can cause compression of the trechea. Additional support that compression occurs might be adduced from the clinical observation that thymectomy and the reduction in size following irradiation of the thymus cause cessation of obstructive symptoms. Morse maintains that this is not an entirely conclusive argument and points out that the thymus shadow on the roentnogram varies continuously, that the symptoms disappear in many instances without treatment, and that the improvement may just as well be due to the disappearance of the real and undiscovered cause. On the other hand, shrinkage of the thymus shadow frequently causes no alleviation of symptoms. The size of the thymus shadow usually bears no relationship to the occurrence of symptoms of respiratory obstruction.

With the aid of modern instruments of clinical study, most of the symptoms of obstruction can now be demonstrated to be due to some other cause: congenital hypotonia of the larynx, obstructive anomalies of the respiratory tract, inflammatory lesions or neoplasms, foreign bodies, enlarged adenoids, atelectasis, bronchiectasis, intracranial hemorrhage, congenital malformations of the heart, tetany and numerous other local and general conditions. "Thymic stridor" is being constantly reevaluated in the light of more complete and more frequent roentgenographic and bronchoscopic examinations, and it has become increasingly clear that enlargement of the thymus plays a minor role in the genesis of respiratory obstruction.

Structures other than the trachea may be compressed. In the bony thoracic inlet the recurrent laryngeal nerves might be compressed by a hyperplastic thymus, and the paresis or

paralysis of the vocal cords resulting from this might be a cause of such symptoms as noisy breathing, stridor or brassy cough. There is the possibility of pressure upon the great vessels and the reduction of their lumen and of cyanosis thereby resulting. The esophagus may apparently also be compressed and this would account for the difficulty in swallowing. Cyanosis of the head, neck and upper extremities could be explained by pressure on the left innominate vein. It is felt, however, by most workers that these symptoms are almost always due to other causes.

The Thymus and Sudden Death: In 1889 Paltauf first described the "lymphatic constitution" which he believed predisposed children to sudden death. Obesity, pallor, hypotonia, generalized lymphoid hyperplasia, and enlargement of the spleen and thymus were characteristic of the condition. Frequently there was hypoplasia of the circulatory system and a thin walled arterial system. The sudden death was a cardiac death, according to Paltauf, and the large thymus produced no signs of local pressure and was no more important as a factor in mortality than the enlarged spleen. This "lymphatic constitution" was quickly and widely accepted, and later the role of the thymus in sudden death was emphasized until the diathesis came to be called status thymicolymphaticus. The causal relationship of the enlarged thymus to sudden death has never been demonstrated, and there has been no agreement on the essential features of this indefinite syndrome. In view of later works, the diagnosis of status thymicolymphaticus on the basis of thymic weight at necropsy seems no longer valid. Interestingly, more than half the healthy young adults who came to necropsy after sudden death in World War I had the morphalogical features of "status thymicolymphaticus." It is clear now that the supposed hyperplasia of the lymphatic system and thymus gland in so-called status thymicolymphaticus is physiological in young, well-nourished individuals.

Apparently healthy infants and children occasionally die following such trivial and usually inadequate causes as slight trauma, minor surgical procedures, emotional excitement and during the administration of anesthetics, vaccines and sera.

In spite of the fact that the theory of status lymphaticus does not explain these fatalities, many clinicians believe that sudden unexplained death is more frequent in infants and children with a pasty, anemic habitus. Evidence available does not justify incrimination of the thymus as a cause of sudden unexpected and otherwise unexplained death. More recent theories of pathogenesis in such episodes include: anaphylactic shock; circulatory collapse in response to either chemical or physical agents; acute adrenal insufficiency with hypoglycemic shock; vagotonia; inadequacy of the sympathetic system; hypoplasia of blood vessels and heart; and cerebral hemorrhage. Necropsies following sudden death are incomplete without blood culture and without careful chemical examination for poisons that kill suddenly.

When the lethal agent in sudden death cannot be established by the chemical and morphologic findings at necropsy, a frank statement that the cause of death is unknown is preferable to the convenient diagnosis of status lymphaticus, which has too frequently served to conceal ignorance of the real cause and inhibited a more exhaustive search for the real cause of death.

Clinical Diagnosis of Thymic Enlargement: The size of the thymus cannot be definitely and satisfactorily determined before death. Palpation of the upper pole of the thymus in the suprasternal notch and percussion of its lateral borders are not reliable. Roentgenographic estimation of its size is probably equally inaccurate. The roentgen diagnosis of enlargement of the thymus is based largely upon an assumed correlation of the size of the thymus with the width of the supracardiac shadow. This assumption is invalid for several reasons.

There are no exact criteria available for the range of normal measurements of the upper mediastinal shadow. Moreover, supposedly pathologically widened supracardiac shadows have been found in 25 to 50% of healthy infants and children. It is of considerable moment that the size of the shadow bears no relationship to the occurrence of symptoms of respiratory obstruction or to sudden death. The supracardiac shadow is a composite of the shadows of several structures in the superior

mediastinum, widening of which may be caused by enlargement or displacement of any or several of its components other than the thymus. Roentgenographically, tracheobronchial lymphadenitis, mediastinal pleurisy, paravertebral abscess, mediastinal neoplasms, pulmonary atelectasis, and anomalous positions of the great vessels may similate enlargement of the thymus.

Furthermore, the width of the supracardiac shadow fluctuates significantly in the same individual under different conditions; it can be altered by a change from the horizontal to the upright position and by inspiration and expiration. Widening occurs in cardiac diastole and during increased intra-abdominal pressure. Facitious widening is frequently caused by a slight oblique position of the patient. X-ray studies for evidence of thymic compression should include a posterior-anterior film taken in the upright position during the two phases of respiration as well as lateral films. At the present time it would seem that clinical symptoms are of as much, if not more, value in the diagnosis of thymic pressure as are roentnograms, unless the latter are taken and interpreted by experts with experience.

Treatment: Partial or total thymectomy is indicated only for new growths of the thymus and has no place in treatment of the ordinary enlargement of it. The only device meriting consideration in treatment of enlarged thymus is X-ray irradiation which was introduced in clinical medicine by Friedlander of Cincinnati in 1907. There is no convincing evidence at the present time to indicate that roentgen irradiation of the thymus will prevent sudden death. As a matter of fact, Waldbott in 1934 recorded three instances in which roentgen treatment for a supposedly enlarged thymus did not prevent sudden death. The routine roentgenographic examination of infants and small children for evidence of enlarged thymus is now rarely practiced, and there is no good reason for routine radiologic treatment of children simply because the roentgenogram suggests thymic enlargement.

Regardless of the theoretical considerations there may be seen at times an apparent cause and effect between radiologic treatment of the thymus and the relief of obstructive symptoms.

If the cause of the obstruction is not found after a thorough examination, including bronchoscopic and roentgenographic investigation, X-ray therapy may be tried empirically. Occasionally unexplained stridor is relieved dramatically in this way, although the mode of operation is obscure.

In conclusion, it seems expedient to quote two authorities in order to reveal a true picture of our present status concerning the thymus gland. Dr. A. G. Mitchell, following an American Academy of Pediatrics panel discussion on the thymus gland in 1939, concluded "whatever knowledge we have gained experimentally concerning the thymus is not applicable in clinical medicine today."

Dr. W. E. Nelson in his new textbook (1945) states "it might be well if the thymus were extended a moratorium of five or ten years from clinical consideration in the hope that further investigation might more accurately determine its true position in pathologic physiology."

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PHARMACOLOGY OF OBSTETRICAL ANALGESIA

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To evaluate quantitatively any pharmacologic series of agents, clearly defined criteria of the desired actions are necessary. There is a divergence of opinion as to these in obstetrical application of analgetics. All obstetrical analgetics pass the placenta and may be potentially dangerous to the infant. There is need both for a moderately potent, long-acting agent with minimal undesired side-effects on mother and infant, and for a highly potent, short-acting agent which is readily controllable.

The antipyretic analgetics are inadequate in obstetrics, since these agents act only to relieve congestive pain, through hemodilution. The salicylates may cause a tendency to hemorrhage, and aminophenol and antipyrine derivatives may interfere with hematopoiesis. These agents should not be used even in combination with the more potent analgetics.

All narcotic agents produce some degree of analgesia as stage I of the anesthetic response. They differ widely in the intensity of their analgetic effect; the barbiturates, for example, are commonly considered to produce very little true analgesia, although large doses may modify the patient's response to pain. Among the aliphatic hypnotics, alcohol and paraldehyde are good analgetics in sub-anesthetic doses. The latter was applied to obstetrical use by Kane and Roth of George Washington University. Paraldehyde may be given by rectum or by duodenal tube in a dose of 30 cc., to produce a moderate analgesia of long duration without causing uterine inertia, or apnea in the fetus. It has a high margin of safety, beyond that of other narcotics. Its chief disadvantages are its persistent excretion, on the breath, which renders the patient obnoxious to others; and the possible expulsion of liquid feces during delivery. Paraldehyde has a uniform effect in contrast with other agents. Severe liver injury may prolong its effects. Avertin and other aliphatic hypnotics are less ideal.

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Intermittent analgesia with inhalation anesthetics is the most effective means of controlling pain in the second stage. N_2O is well suited to obstetric use because of its extreme rapidity of action. Precautions must be taken to avoid anoxia, but analgetic tensions are well below those producing anoxia and a skilled anesthetist need never exceed these. More potent anesthetics are not required, since as good analgesia is obtained with N_2O without danger of explosions. Cost of semi-open, intermittent anesthesia is also a factor in favor of N_2O analgesia. For home practice, vinethene (divinyl oxide) is superior to ether because it is more rapid, and is superior to chloroform since it produces minimal liver damage if the patient is kept well oxygenated.

Morphine and dilaudid are potent analgetics but are also among the most potent respiratory depressants known. On pharmacologic grounds, their use in obstetrics is undesirable. However, small doses may be necessary. The dose should never be increased beyond 8 mg. Animal experiments with the fetus in utero indicate that small doses of morphine have less effect on respiratory movements than do the barbiturates. Hyoscine (scopolamine) is not an analgetic, and should be used in doses not exceeding 0.4 mg. to produce amnesia.

The most recent innovation in obstetrical analgesia is the use of demerol (dolantin, pethidine), the ethyl ester of 1-methyl-isonipecotic acid. The synonym isonipecaine denotes the chemical nature of this material. British workers introduced this agent as an obstetrical analgetic after it had been used in Europe as an antispasmodic narcotic. The small dose of 50 mg. used originally in obstetrics is followed by moderate analgesia of long duration in most patients. Side-effects, seen particularly with larger doses, include excitement, nausea, vomiting, and vertigo. Occasionally large doses may cause uterine relaxation. Pharmacologic studies have been made by Gruber et al. (Jour. Pharmacol., 73:319, 1941), and Yonkman et al. (Ann. Intern. Med., 31:7, 1944). The Ld_{50}, in mg./kg., is 147 i.p., and 221 oral, for mice; 93 i.p., for rats; 32 i.v., for small rabbits and 20 i.v., for large rabbits. Death is due to respiratory failure. Peripheral vasodilatation follows the i.v. injection of even

minute doses in dogs, with a fall in blood pressure. Demerol has a weak atropine-like action and also a weak papaverine-like action. It antagonizes the effects of epinephrine and musculotropic agents on the isolated intestine, and causes a relaxation of most smooth muscle to a lesser extent than papaverine or the barbiturates. In the intact dog, but not in man, demerol causes spastic contraction of the small intestine. It may have a constipating effect in man. Demerol usually stimulates the intact or isolated uterus, but may occasionally cause relaxation. In clinical use, small doses do not seem to delay labor, while affording moderate alangesia. Yonkman states that in man 100 mg. produces more analgesia than 60 mg. of codeine, but less than that produced by 15–30 mg. of morphine. Himmelsbach, at the Federal Narcotic Hospital in Lexington, Ky., finds that demerol is addictive, according to his criteria of addiction; but it is less addictive than morphine. Euphoria sometimes occurs after therapeutic doses.

Demerol is of particular pharmacologic interest since it is the first simple compound shown to have a potent analgetic effect. Other simple agents which might have the same potency without the undesirable side-effects of demerol are anticipated.

None of the analgetics used in obstetrics is ideal for the purpose and all must be used cautiously to make an unbearable pain tolerable rather than to abolish it. Much can be done to minimize pain by proper pre-operative management and by reassuring the patient. Nitrous oxide analgesia permits good oxygenation of the patient if properly handled, and produces a safe, effective alangesia. Nerve block anesthesia is best reserved for the complicated case in which the ordinary analgetics are contraindicated. In any instance, use of the analgetics must be adapted to the individual patient. There is no routine obstetric analgetic procedure which can be recommended on a pharmacologic basis.

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GASTROSCOPIC FINDINGS IN CHRONIC DUODENAL ULCER*

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A gastroscopic study of patients with proven chronic duodenal ulcer is undertaken to determine whether an associated chronic gastritis has any clinical significance. The problem has its theoretical aspects especially as it concerns the pathogenesis of peptic ulcer. Furthermore, such a study is another clinical approach by which the gastroscopic picture of chronic gastritis may be evaluated.

The claim that gastritis and gastro-duodenitis is an universal precursor to the development of chronic peptic ulcer is not generally accepted by all clinicians (Bockus, 1943). Those who advocate this theory (Konjetzny, quote Faber, 1935; Faber, 1935; Hurst, 1933; Simpson, 1935; Hebbel, 1943) base their views upon the demonstration of antral gastritis and a gastro-duodenitis in every stomach surgically resected for peptic ulcer. Walters and Sebening (1932) found ulcerative lesions in the antrum of similarly resected specimens only rarely. There is some doubt expressed as to the significance of these changes in resected stomachs since they may be the result of operative trauma (Schindler, Necheles, and Gold, 1939; Sanders and Mecray, 1941). Gastroscopists, such as Schindler (1937), have not observed gastritis in all patients with peptic ulcer. Furthermore, the development of chronic peptic ulcer in a primary gastritis has not been observed by gastroscopic examination. The present day conception of this problem, as stated by Bockus (1943), is that in some instances peptic ulcer may result from a severe primary gastritis, but it is improbable that a great number of simple peptic ulcers are the result of this mechanism.

A survey of the literature shows that gastritis occurs with greater frequency in patients with duodenal ulcer than it does

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in the general population subjected to gastroscopic studies. Schindler (1939) reports an incidence of 41.8 per cent for chronic gastritis. In 700 gastroscopic examinations, Carey (1940) finds primary gastritis in 44.0 per cent. A much lower incidence, namely, 12.0 per cent in 240 patients, is reported by Ruffin et al. (1940). The incidence of chronic gastritis found in duodenal ulcer patients varies from 40.0 per cent (Montgomery et al., 1944) to 74.0 per cent (Scheff et al., 1944). From the literature, reports of gastroscopic examinations of 531 patients with duodenal ulcer show chronic gastritis in 332 patients or 62.5 per cent. (Table I.)

TABLE I

Incidence of Chronic Gastritis Associated with Chronic Duodenal Ulcer.

Author	Total Cases	No. with Gastritis
Templeton and Schindler (1939)	64	40
Christiansen (1940)	70	49
Carey and Ylvisaker (1942)	70	37
Letendre and Schindler (1942)	171	99
Tumen and Lieberthal (1943)	50	33
Montgomery et al. (1944)	20	8
Scheff et al. (1944)	50	47
Cutler and Walther (1945)	36	19
Total	531	332

Percentage Incidence—62.5.

There is no uniformity in the type of gastritis found with duodenal ulcer with the exception of the atrophic variety which appears to be the least common. The highest incidence of atrophic gastritis in any series of duodenal ulcer cases reported in the literature is 10.0 per cent (Tumen and Lieberthal, 1943). Carey and Ylvisaker (1942) found none in their series of 70 patients. A majority (Templeton et al., 1940; Christiansen, 1940; Scheff et al., 1944) report the incidence of this type to be less than 5 per cent. Hypertrophic gastritis has been found in 10.0 (Scheff et al., 1944) to 38.5 per cent (Carey and Ylvisaker, 1942) of patients with duodenal ulcer. Just as great variation for the occurrence of superficial gastritis is observed in these ulcer cases where the lowest reported incidence rate is 21.9 per cent (Templeton and Schindler, 1939)

and the highest, 62 per cent (Scheff et al., 1944). Antral gastritis has been found infrequently. Christiansen (1940) did not observe such changes in 70 patients with duodenal ulcer. Carey et al. (1942) found gastroscopic evidence of antral gastritis in 11 of a group of 70 duodenal ulcer patients. The technical difficulty in obtaining a satisfactory view of the antrum through the gastroscope may account for the infrequency with which antral gastritis is found.

There is no uniform opinion expressed in the literature as to the clinical significance of these gastroscopic changes observed in patients with duodenal ulcer. Carey and Ylvisaker (1942) conclude that patients with chronic duodenal ulcer and gastritis tend to develop chronicity, intractability and recurrence of symptoms. Retention, hemorrhage and perforation occur with essentially the same frequency in both the gastritis and non-gastritis groups. They suggest that gastroscopy is of value in patients with chronic duodenal ulcer if the disease is refactory, chronic or recurrent or if operation is contemplated.

Tumen and Lieberthal (1943) thought that the incidence of atypical histories and poor therapeutic response were somewhat greater among duodenal ulcer patients with gastritis but they observed that patients with normal stomachs at gastroscopic examination could have the same atypical symptomatology and poor response to therapy. Evaluation of the clinical significance of gastritis was difficult in these cases because among 21 ulcer patients with gastritis gastroscoped 2 or more times, the clinical severity of the symptoms seemed related to the extensiveness and degree of mucosal change in only 10 patients. The remaining 11 patients showed no such relationship. The presence of gastritis did not regularly influence the clinical course of duodenal ulcer. In some individual cases it might have added to the severity of the symptoms; in others it was present in a symptomless manner. They were unable to postulate the presence or absence of an associated gastritis in their patients on the bases of the nature of sypmtoms or character of response to therapy.

Cutler and Walther (1945) note as favorable a response to an ulcer regimen in 19 patients with duodenal ulcer and associated gastritis as occurs in 20 similar patients with normal stomachs.

Palmer (1942) believes that there is no relationship between the symptomatology and the presence or absence of gastritis in peptic ulcer. With an adequate ulcer regimen, there are no symptoms even though the gastritis persists. Bockus (1943) states that gastritis in association with an active ulcer "must be looked upon as adding further gravity to the prognosis insofar as permanent cure is concerned." Eusterman (1936) thinks that only when a gastritis is marked in cases of duodenal or gastric ulcer is it justifiable to attribute symptoms or failure of therapeutic measures to the gastritis. He cautions against attributing too much significance to minor gastroscopic changes.

Summarizing this review of the literature, one may conclude that chronic gastritis occurs commonly with duodenal ulcer. Antral gastritis has been observed but infrequently in these patients at gastroscopic examination. There is no characteristic clinical syndrome by which those ulcer patients with gastritis can be diagnosed except by gastroscopy. The clinical significance of the gastritis as it is related to therapeutic response and to prognosis is uncertain.

Method of Study

A group of 46 patients, each with X-ray evidence of either an active duodenal ulcer or a deformed duodenal bulb, is selected for this study. None of this group had evidence of retention. The patients are classified as to the presence or absence of clinical activity of the ulcer at the time of gastroscopic examination. A history of acute gastric distress and the demonstration by X ray of a tender, deformed irritable duodenal bulb with or without a crater constitute the criteria for activity. A deformed duodenal bulb without tenderness as demonstrated by X-ray procedures and/or the absence of acute ulcer distress are considered as evidence for inactivity in those patients whose past history is compatible with the diagnosis of duodenal ulcer. The presence or absence of typical

ulcer pain is noted in each case history. A patient is considered to have typical pain if the abdominal distress is rhythmical and is relieved by food or alkalies. Arhythmicity of symptoms or the absence of relief from food or alkalies are considered atypical. The occurrence of hematemesis as the presenting symptom of a duodenal ulcer demonstrable by X ray is classified as atypical. The gastroscopic examinations were done in a majority of these patients within two weeks after the therapeutic regimen had been started. In 3 patients, this examination preceded the institution of therapy. Some of the gastroscopic examinations were done by Dolf L. Curb.* All the patients were either admitted to the Medical Service of the John Sealy Hospital or examined in the Medical Outpatient Clinic.

The response to a routine Sippy regimen of ulcer therapy is evaluated for each patient first as to the promptness with which symptoms are controlled and second, as to the recurrence of symptoms subsequent to the time of gastroscopic examination. The response to therapy is considered satisfactory if the symptoms subside promptly and if there are no subsequent recurrences. Poor therapeutic response or recurrence of symptoms is considered unsatisfactory.

Data

Of the 46 patients, 37 had active duodenal ulcer and 9 had inactive ulcer at the time of gastroscopic examination. Chronic gastritis was observed in 26 patients or 56.6 per cent of the series (Table II). The types of chronic gastritis are (1) hypertrophic gastritis in 19 individuals or 41.3 per cent; (2) atrophic gastritis in 3 patients, or 6.5 per cent; (3) superficial gastritis in 2 or 4.3 per cent; and (4) mixed gastritis in 2 or 4.3 per cent. Antral gastritis was observed in 3 patients. In two it was of the hypertrophic variety and in the third, it was a superficial type. The latter patient also showed a patchy atrophic gastritis.

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The symptomatology presented by 19 patients with active ulcer symptoms and a chronic gastritis is very similar to that given by 18 patients with like symptoms and no gastroscopic evidence of gastritis (Table II). Males predominate over fe-

TABLE II

A. *Active Duodenal Ulcer.* (At time of Gastroscopic examination.)

	Normal Stomach		Chronic Gastritis		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total Number Patients	18	48.7	19	51.3	37	100.0
Males	15	83.4	15	78.0	30	81.1
Females	3	16.6	4	22.0	7	18.9
White	11	61.2	9	47.3	20	54.0
Negro	7	38.8	10	52.7	17	46.0
Average Duration Symptoms	6.8 yrs.		9.4 yrs.			
Average Age Years	43.9 yrs.		43.8 yrs.		43.8 yrs.	
Symptomatology						
Typical pain	13	61.6	15	78.9		
Atypical pain	5	38.4	4	21.1		
Nocturnal pain	8	44.4	13	68.4		
Nausea; and/or emesis	14	77.8	13	68.4		
Belching; Flatulence	9	50.0	10	52.7		
Hematemesis	0	00.0	2	10.5		
Melena	2	27.8	3	15.8		
Radiation of pain	8	44.4	5	26.3		
Pain located other than epigastrium	2	11.1	3	15.8		
B. *Inactive Duodenal Ulcer.* (At time of Gastroscopic examination.)						
Total Number Patients	2	41.7	7	58.3	9	100.0
Males	1	50.0	6	85.5	7	77.7
Females	1	50.0	1	14.5	2	22.3
White	1	50.0	5	71.4	6	66.6
Negro	1	50.0	2	28.6	3	33.4
Average Duration Symptoms	3.8 yrs.		11.3 yrs.			
Average Age Years	57.0 yrs.		49.2 yrs.		51.0 yrs.	
Symptomatology						
Typical pain	1	50.0	3	44.4		
Atypical pain	1	50.0	4	55.5		
Nocturnal pain	1	50.0	5	77.7		
Nausea; and/or emesis	1	50.0	6	85.5		
Belching; Flatulence	2	100.0	2	28.5		
Hematemesis	0	0.0	0	00.0		
Melena	0	0.0	0	00.0		
Radiation of pain	0	0.0	3	44.4		
Non-epigastric pain	0	0.0	3	44.4		
C. Summary Gastroscopic Findings Uncomplicated Duodenal Ulcer.						
Total Number Patients	46					
Normal Stomach	20 or 43.4%					
Chronic Gastritis	26 or 56.6%					

males in a ratio of 5 to 1 in each of these two groups. Although the average age is 43 years respectively for each group, the

average duration of symptoms is 9.4 years for those with gastritis and 6.8 years for those with normal stomachs. Typical ulcer pain is found with slightly greater frequency in the gastritis group (78.9 per cent) than it is in the normal group (61.6 per cent). There is no significant difference in the occurrence of atypical pain in either group. Nocturnal pain occurs in 13 or 68.4 per cent of the individuals with gastritis and in only 44.4 per cent of the non-gastritis ulcer patients. Symptoms which might suggest a primary chronic gastritis, e.g., nausea, vomiting, belching, flatulence, diffuse epigastric pain are found no more frequently in those with gastritis and duodenal ulcer than in the patients with normal gastroscopic findings. There is little difference in the free and total acidity of the fasting gastric secretions between the two groups.

Of the 9 patients with inactive duodenal ulcer, 7 had gastroscopic findings compatible with a diagnosis of chronic gastritis and 2 showed normal stomachs. The average duration of symptoms in the gastritis group is 11.3 years. The average age 49.2 years. One of the control patients was 44 years of age and had symptoms for 1½ years; the other was 70 years of age and symptoms had been present for 6 years. The frequency of atypical pain in the gastritis group is 55.5 per cent. Seventy-eight per cent, complained of nocturnal pain. The above symptoms occurred during previous admissions to the hospital. Several patients who showed X-ray evidence of a deformed duodenal bulb and normal stomachs at gastroscopy were excluded from this study because either there was other organic pathology which could account for symptoms or else the possible existence of these factors had not been sufficiently ruled out. Atypical pain and nocturnal pain occurred with equal frequency in the 2 patients with normal stomachs.

No correlation is found in these 46 patients between the gastroscopic findings and the symptomatology. Neither is there any apparent relationship between the extent and severity of the gastritis observed and the patient's symptoms. For example, of the 14 patients with hypertrophic gastritis and active ulcer, 5 had severe or marked mucosal changes; the other 9 patients had mild or patchy hypertrophic gastritis. Complaint of night

pain was made by 3 of the 5 patients with the severe gastritis. There was no mention of night pain in the case record of the fourth patient and the fifth had no nocturnal pain. All of the 5 individuals had typical pain. Only 1 previously had severe hemorrhage. Among the 9 patients with mild changes, 2 had severe hematemesis, 2 had atypical pain, and 7 mentioned the occurrence of nocturnal pain. This lack of correlation between symptoms and gastroscopic findings is characteristic for patients with the other types of gastritis in this series.

A second gastroscopic examination in 7 patients done 2 to 48 months after the first endoscopy offers opportunity to observe whether any variation in the extent or type of gastritis occurs within the passage of time. Five patients had hypertrophic gastritis at both examinations. In 3 of this group, the mucosal picture appeared the same at each of the two examinations. One of these patients was rescoped after 3 months of ulcer therapy. Although the gastroscopic picture remained unchanged, the patient had symptoms at the time of the first study and no symptoms at the time of the second gastroscopy. The other 2 patients were re-examined at 22 and 48 months respectively after the first endoscopic study. The ulcer was active at the time of the original examination and inactive at the time of the second in 1 patient. In the other individual, it was active at the time of both examinations. The hypertrophic gastritis was thought to be less marked after a second gastroscopy in 2 other patients. One of these responded poorly to routine ulcer management and had frequent recurrence of symptoms. Although a second gastroscopy 2 months after the first study was thought to show less marked hypertrophic manifestations, the patient's condition was clinically unimproved. A subtotal resection was done 18 days after the second gastroscopy. The patient made an uneventful recovery and remained symptom free for a little over 7 months that he was observed post-operatively. The gastroscopic findings were confirmed by the pathologist. A second case in which the hypertrophic changes were thought to show improvement was sympton free at the time of the second examination, 8 months

after the first study. In spite of this improvement, his subsequent course was characterized by rather frequent recurrences of symptoms.

Superficial gastritis was observed in 1 patient, on 2 occasions, 48 months apart. During this interval of time, the patient was never constantly symptom free because he would not follow his diet. The gastritis appeared to be essentially the same at both examinations.

An atrophic gastritis with erosions was found, 46 months later, to show a superficial gastritis in the antrum and a patchy atrophic gastritis of the anterior wall of the body. This patient had followed her diet faithfully during the intervening time. She had 2 relapses during this time. The precipitating factor in the last exacerbation appeared to be worry.

The evidence presented above suggests that chronic gastritis associated with duodenal ulcer does not change markedly in spite of therapeutic measures directed towards control of the ulcer symptoms. Mucosal erosions will heal with such therapy. In none of these cases has the gastritis appeared to progress in severity, but the number of cases is too small to draw any conclusions.

The presence of gastritis with duodenal ulcer in this series of 46 cases does not significantly affect the response to therapy (Table III). Eleven patients were observed for the period of

TABLE III

Response to Therapy

	NORMAL STOMACH					CHRONIC GASTRITIS				
		Relapse					Relapse			
No. Years Follow-up	Total Symptom Free	Adherence to Diet Yes	No	Total Relapse	Per Cent	Total Symptom Free	Adherence to Diet Yes	No	Total Relapse	Per Cent
0	5	0	0	0	0.0	5	1	0	1	16.5
0–1	3	1	0	1	25.0	4	1	1	2	33.3
1–3	3	1	2	3	50.0	3	2	1	3	50.0
3–5	1	1	3	4	80.0	1	3	4	7	87.5
Total	12	3	5	8		13	7	6	13	
Percentage	60.0	15.0	25.0	40.0		49.9	26.9	23.0	50.1	

hospitalization only. Only 1 of the entire group did not have a prompt remission of symptoms. This patient had a patchy area of atrophic gastritis on the anterior wall of the stomach.

It is doubtful that such a minor mucosal variation from normal is responsible for the poor response therapeutically.

Twenty-five per cent of 4 patients with a normal stomach and 33.3 per cent of 6 individuals with chronic gastritis, followed for less than one year after gastroscopy, had recurred of symptoms. In two, one with gastritis and one with a normal stomach, factors other than non-adherence to the diet were responsible for the relapse.

Six patients with normal stomachs and 6 with chronic gastritis were observed from 1 to 3 years. Exactly 50.0 per cent of each group had a recurrence of symptoms. Two of those with normal stomachs and one with gastritis, the exacerbation was due to dietary indiscretions.

In the group followed from 3 to 5 years, 80.0 per cent of 5 patients with normal stomachs and 87.5 per cent of 8 showing gastritis had a relapse with return of symptoms. Three of those with gastroscopic changes and 1 without such a picture were observing their ulcer diet at the time of recurrence.

In summary, the response to therapy of 20 patients with duodenal ulcer and normal stomachs at gastroscopy is satisfactory in 60.0 per cent (12 patients) and unsatisfactory in 40.0 per cent (8 patients). Thirteen or 49.9 per cent of 26 patients with duodenal ulcer and chronic gastritis had a satisfactory response to therapy. An unsatisfactory one occurred in 13 or 50.0 per cent. Relapse was attributable to factors other than dietary management in 3 or 15.0 per cent of normal group and in 7 or 26.9 per cent of the chronic gastritis group. Non-adherence to diet was responsible for recurrence of the disease in 25.0 per cent of those with normal stomachs and 23.0 per cent of those in whom there was gastroscopic evidence of gastritis. While this evidence does not conclusively prove that an associated gastritis in duodenal ulcer always makes the latter disease more refractory to therapeutic control, it does suggest that such may occur in individual patients with the associated diseases.

Discussion

There appears to be a much higher incidence of chronic gastritis associated with chronic duodenal ulcer than is found

in the general population. Thus, in 432 gastroscopic examinations done at The University of Texas Medical School, 160 or 37.1 per cent had normal stomachs. Chronic gastritis was observed in 182 or 42.0 per cent. These figures compare favorably with those reported by Schindler (1939) and Carey (1940). The incidence of chronic gastritis in 46 patients with uncomplicated duodenal ulcer is 56.6 per cent. Evidence is cited above to show that the incidence of chronic gastritis in 531 duodenal ulcer patients studied gastroscopically and reported in the literature is 62.5 per cent. While these figures emphasize the common occurrence of chronic gastritis, they also point out that gastritis is not observed by the gastroscopist in 100 per cent of duodenal ulcer patients. Furthermore, the antrum of the stomach is seldom observed to be the site of such changes. This appears to be in direct contradiction to the histological findings seen in surgically resected stomachs in every case so studied (Konjetzny, quote Faber, 1935; Hebbel, 1943). The poor correlation between gastroscopic findings and the histological picture as demonstrated by Swalm and Morrison (1941) and Benedict and Mallory (1943) may explain in part the reason for this contradictory evidence. Other factors are (1) the lack of universal criteria for a histological diagnosis of a normal stomach (Bockus, 1943); (2) the effect of operative trauma on resected stomachs (supra vide); and (3) the limitations of the gastroscope which prevent close visualization of the antral mucosa. On the other hand, the infrequency of antral gastritis and the presence of normal stomachs in 40.0 per cent of duodenal ulcer cases examined gastroscopically does suggest that gastritis may be secondary to the development of duodenal ulcer.

What is the clinical significance of these gastroscopic findings in duodenal ulcer? The literature reviewed and the evidence accumulated from this study suggest that little difference in symptomatology exists between doudenal ulcer patients with gastritis and those with no visual evidence of mucosal pathology. A possible exception to this statement is the more frequent occurrence of nocturnal pain in this series of cases with the associated gastritis. This symptom, by itself, is not of cardinal

diagnostic value since it is present in 44.0 per cent of the ulcer patients with normal stomachs. With the possible exception of primary hypertrophic gastritis, chronic gastritis not associated with duodenal ulcer manifests the same poor correlation between the gastroscopic findings and the clinical symptoms although Bockus (1943) states that "certain clinical trends may be assigned to the types of gastritis defined by the gastroscopist." Others, such as Palmer (1942), believe that there are no clinical symptoms due to chronic simple gastritis but that ulcerative gastritis may have a ulcer-like distress. In view of this inability to assign a definite clinical symptomatology to chronic gastritis in general, and in view of the fact that the hypertrophic variety often manifests a peptic ulcer-like syndrome, is it logical to expect the association of chronic gastritis with duodenal ulcer to present a clinical syndrome by which it can be differentiated from duodenal ulcer without such changes?

The duration of symptoms is longer in the gastritis group in this study than it is in the normal group. This suggests that the occurrence of gastritis with duodenal ulcer may favor chronicity. On the other hand, it may mean only that the factors which promoted chronicity in doudenal ulcer also favor the development of chronic gastritis. Much more extensive research is needed before this problem can be answered.

The impression is gained from a survey of the case histories of the 46 patients with duodenal ulcer in this series, that certain patients with a gastritis are often more difficult to manage therapeutically. The more frequent occurrence of exacerbation of symptoms while under dietary management in those ulcer patients with gastritis suggests that poor response and recurrence of the disease may be due to the gastritis. On the other hand, relapse of symptoms due to non-adherence to the diet is no more frequent in the gastritis than it is in the non-gastritis patients of this series.

The evidence presented above, then, does not conclusively prove that gastritis associated with duodenal ulcer either significantly affects the clinical course of the disease or markedly

alters the therapeutic response. It is believed that if the therapeutic management of a duodenal ulcer case is adequate, the patient should remain symptom free regardless of whether an associated gastritis is present or not. It is likewise recognized that in some individual cases, the presence of a gastritis may necessitate a more strict regimen of therapy than is given for the usual ulcer patient. In such a patient, the presence of gastritis may be of some clinical significance. In most patients with duodenal ulcer the demonstration of a chronic gastritis has little clinical significance.

Conclusion

1. The incidence of chronic gastritis as determined by gastroscopic examination of 46 patients with uncomplicated duodenal ulcer is 56.6 per cent.

2. No clinical syndrome is postulated by which the presence or absence of chronic gastritis can be ascertained in patients with duodenal ulcer. The diagnosis can be made only by gastroscopic examination.

3. The association of chronic gastritis with duodenal ulcer may, in certain cases, promote chronicity, poor therapeutic response and frequent recurrences, but in a majority of the patients, this association appears to be without clinical significance.

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ANTI-RICKETTSIAL ACTIVITY OF PARA-AMINO-BENZOIC ACID (PABA)

Evaluation and Significance of PABA Blood Levels in Guinea Pigs with Reference to Spotted Fever Treatment*

Ludwik Anigstein and Dorothy M. Whitney

The coördinated and accelerated research of the war period resulted in an unprecedented progress in various fields of science. Among the advances in medicine those in prevention and chemotherapy of infectious diseases were particularly significant. While the newly developed vaccines gave us efficient means of protection against typhus and spotted fevers, the specific therapy of these diseases still awaits solution. It is of interest to note that the otherwise beneficial sulfonamide therapy proved not only unsuccessful but also harmful when applied to rickettsial infections. This failure led Snyder, Mier and Anderson (1942) to attack the problem from an entirely different angle. Their concept was based on the premise that the "antagonism between the sulfa drugs and PABA in bacterial growth might be present in rickettsial infections in the reverse direction."

This logical assumption was the starting point of investigation of a possible beneficial effect of PABA on rickettsial infections and, as it seems, the opening of a new chapter in the chemotherapy of this group of diseases.

The beneficial effect of PABA in the treatment of louse-borne typhus by the U. S. A. Typhus Commission in Egypt (Yeomans, Snyder, Murray, Zarafonetis and Ecke, 1944) as well as the demonstration of its rickettsiostatic action in egg-yolk sac cultures (Greiff, Pinkerton and Moragues, 1944) justified the extension of PABA application to other rickettsial infections.

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Successful results were obtained by Anigstein and Bader (1945) in guinea pigs infected with spotted fever and treated by oral administration of PABA. When 2% of the drug was incorporated into the diet beginning with the day of infection about 80% of the guinea pigs either did not develop any fever or reacted with slight attacks and recovered. All the control animals developed typical spotted fever and died.

Thus it has been established by previous investigations that PABA exerts a rickettsiostatic action in human and experimental rickettsial infections. However, this effect can only be achieved when large or even excessive dosage of the drug is used. Pharmacologic properties of PABA, namely, the rapid absorption and elimination from the body and the ease of its conversion into the inactive conjugated form are the critical factors in PABA therapy.

While the mechanism of PABA action on rickettsiae is still obscure and offers a wide field for speculation, the most evident and tangible criteria are the actual concentration of the drug *in vivo* and its effect on the host.

As examples: Concentration of PABA in the blood of typhus patients between 10 and 20 mg. per cent was considered satisfactory by Yeomans, Snyder, Murray, Zarafonetis and Ecke (1944), while in the human case of Rocky Mountain spotted fever treated successfully by Rose, Duane, Fishel (1945) a PABA level of only 6.6 mg. per cent established during the first day of treatment was followed by a rapid decline of fever and alleviation of symptoms. Otherwise, only fragmentary data as to PABA values in the blood of infected host are available. This applies particularly to the problem of correlation between PABA values in the infected host and the course of infection.

The present study is an attempt to cover certain phases of this problem and their possible practical implications.

Material and Methods

Throughout the study guinea pigs (450–600 gm. body weight) were used. A highly virulent strain of Rocky Mountain spotted fever of tick origin was maintained in guinea pigs by transfer, using spleen suspensions in skimmed milk

as inoculum. In the great majority of the control series the incubation period was 72 hours, but in sporadic instances short incubations of 48 hours were observed. The height of the abrupt fever elevation was usually reached on the third or fourth day ranging between 40° C and 41° C, subsiding within the next two or three days.

The average duration of fever in the untreated animals was 5–6 days. In the majority of male guinea pigs a typical scrotal swelling with purple discolorations and frequent necrosis of the scrotum was noted. The fatality rate of the untreated guinea pigs was 100 per cent.

As a whole, PABA was administered orally, but in several series the drug in its soluble sodium salt was given parenterally by subcutaneous or intra-abdominal routes. Because of the relative insolubility of the acid, its sodium salt-paraaminobenzoate (NaPAB) was used. It was prepared by the addition of 500 ml. distilled water to 84 gm. of sodium bicarbonate and 137 gm. of PABA (Murray, Zarafonetis and Snyder, 1945). The resulting brown solution was evaporated and the residual powder was then readily soluble in distilled water. Solutions of NaPAB in various strengths of 10, 20, and 30 per cent were used for injections.

The oral administration was carried out either by compulsory feeding of the drug or by voluntary intake of PABA in the diet. The drug used in forced feeding was supplied either in the soluble sodium salt or in suspension of the insoluble acid in such vehicles as acacia, tragacanth and colloidal aluminum hydroxide ("Amphojel"). The concentration of the drug in solutions or suspensions varied from 15 to 30 per cent, the dosage being 1–2 ml. three times a day. The total daily dosage in forced feedings ranged between 0.45 gm. to 1.8 gm. per guinea pig. Finally, the treatment by natural intake consisted of diet (coarse chopped cabbage and carrots) to which from 1 to 2 per cent of PABA powder was added.

In the early experiments the protein supply was provided by addition of 5 per cent of casein (vitamin free) but later 5 per cent of soya flour was found more satisfactory. Recently the content of soya flour was increased to 10 per cent. In

addition, 2 per cent of calcium gluconate was added to the diet. The usual daily amount of food at the disposal of each guinea pig was 100 gm. which contained 2 gm. PABA, 10 gm. soya flour (40 per cent protein) and 2 gm. calcium gluconate. Single guinea pigs were kept in separate cages, the residual food was weighed on the following morning, whereby the 24 hours intake of the drug could be approximately calculated.

METHOD FOR DETERMINATION OF PABA IN BLOOD:

a. *Principle.* The method used in the determination of PABA levels is based on the Bratton and Marshall procedures for sulfonamide compounds (1939). This method was modified by one of us (D. M. W.) for small amounts of blood (0.15 ml.). The Klett-Summerson photoelectric colorimeter was used. The method for determining the "total" PABA is based on the Bratton and Marshall principle and likewise adapted to our purpose (Maher, 1944).

b. *Reagents and Materials.* Pipettes. Blood collecting pipettes calibrated to 0.15 ml. were fitted with small rubber tubing and mouthpiece.

Potassium oxalate 20%.

Sodium nitrite 0.2%, renewed daily.

Ammonium sulfamate solution 2%.

Color reagent—0.1% aqueous solution of N–(1–naphthyl) ethylene-diamine-dihydrochloride — Eastman Kodak Company.

Hydrochloric acid (approximately 4N).

Stock standard p-aminobenzoic acid solution. In 500 ml. volumetric flask dissolve 100 mg. of the compound, dilute to mark and mix. (1 ml. equals 0.2 mg.)

Trichloracetic acid 15%.

c. *Preparation of Standard Curve.* 5 ml. of stock standard is diluted to 100 ml. with distilled water (1 ml. equals 0.01 mg.). From this a series of standards containing 0 to 0.4 mg. per cent were prepared. These solutions in samples of 1.0 ml. were diazotized and coupled as described in (d), then placed in the colorimeter and readings taken. These readings were plotted on semi-

logarithmic paper. Concentrations of PABA in the plasma filtrates can be determined by diazotizing, coupling and translating into PABA using the standard curve.

d. *Procedure.* The guinea pig's ear was cut through the marginal ear vein, the ear wiped with cotton slightly dampened with potassium oxalate solution, and the blood collected in the pipette (rinsed out with the oxalate solution and blown dry). The blood was placed directly into 2.85 ml. distilled water in the centrifuge tubes. After hemolysis, 0.75 ml. of 15% trichloracetic acid was added. The tubes were shaken and allowed to stand 15 minutes, then were centrifuged to throw down the precipitated proteins. It is highly important that the filtrate be colorless and clear. The dilution of the blood at this point is 1 to 25.

Determination of "free" PABA:

1 ml. of the filtrate was placed in a standard Wasserman test tube and 1 ml. distilled water added. 0.1 ml. sodium nitrate was added and the mixture allowed to stand ten minutes. 0.1 ml. ammonium sulfamate solution was added and allowed to stand three minutes. 0.1 ml. of the color reagent was added and the color allowed to develop to its fullest intensity, about fifteen minutes, before reading in the photoelectric colorimeter. Proper dilutions should be made according to the expected readings.

Determination of total PABA and conjugated PABA:

1.0 ml. of the blood filtrate was placed in a test tube calibrated to 2 ml. 1.0 ml. distilled water and 0.1 ml. of 4NHCl was added. The solution was kept in a constantly boiling water bath for one hour and distilled water added from time to time to the 2 ml. level. At the end of the one hour period, the tubes were cooled, made up to volume and in the same tube diazotized as described above. The figure obtained from the colorimetric reading represents the total mg. per cent

of PABA, and by subtracting the free PABA determination, the conjugated values can be obtained.

RESULTS:

Parenteral administration of PABA. The first group of six guinea pigs was injected with 3 cc. of 10 per cent NaPAB in saline three times a day totaling 0.75 to 0.9 gm. daily. This treatment was continued for seven days covering the febrile period of the control animals. The blood plasma determinations of diazotizable substance (DS), hereafter referred to as PABA, were made after 1, , 4 and 6 hour periods following the first injection. The highest PABA values were recorded at the end of the first hour—10 mg. per cent (average) with a decline to an average of 1.7 mg. per cent at the end of the second hour. No trace of DS was found after 4 hours but an average of 1.1 mg. per cent of DS was found after the 6 hour period.

The second series of six guinea pigs was injected with 20 per cent NaPAB in saline subcutaneously at the dosage of 4 mg. NaPAB per 100 gm. body weight. The daily total was 480 to 720 mg. of the sodium salt per guinea pig. The treatment began simultaneously with the infection and was continued over the incubation period and the first three days of fever of the control. Blood samples were taken at two and four hour intervals. As a whole the DS values were inconsistent and on a relatively low level ranging between 0.1 mg. per cent and 12.3 mg. per cent (expressed as PABA). A prolongation of the incubation to five days was observed in the treated guinea pigs. Two animals showing high PABA levels although running typical fever recovered, while all the controls died.

The third series of twelve guinea pigs treated with 30 per cent NaPAB for 4 days following the infection exhibited a drastic increase in PABA levels, namely 34 mg. per cent (average) 30 minutes after the first injection, and 18 mg. per cent at the end of two hours. In one case a level of 43 mg. per cent was reached one hour after injection. Negligible levels (average 0.9 mg. per cent) were found at the end of four hours. Except for a three day delay in the onset of fever, no effect on the course of the infection was noted. All guinea pigs died.

The analysis of the above observation shows that the parenteral route of PABA administration although producing at times high levels in the blood had practically no influence on the course of spotted fever infection. It is true that in the majority of guinea pigs a prolongation of the incubation period indicates a partial suppressive action of the drug in the early stages of the infection, however, under these conditions the development of the disease could not be checked. It is not improbable that the administration of the drug at more frequent intervals would enhance the suppressive action of PABA. However, the damaging effect of the inoculation of NaPAB, namely, subcutaneous and abdominal hemorrhages, render such multiple dosage impracticable.

Oral Administration of PABA

a. Compulsory.

The drug was administered in various forms: as soluble 15 per cent NaPAB (Chart 1) and in 15 per cent suspensions of PABA powder in a 1.25 per cent aqueous solution of gum tragacant. Finally, the alumina gel "Amphojel" (Wyeth, Inc.) was used as vehicle carrying 15 per cent of PABA powder. In each of these modifications 3 ml. were given 3 times during 24 hours to each guinea pig, beginning with the day of infection. The treatment was continued for five consecutive days. All twelve guinea pigs of this series developed characteristic spotted fever. There were five survivals as compared with no survivals among the controls. No differences could be noted as to the superiority of any form of the drug.

As to the PABA levels in the blood, the highest values were recorded at the end of the first and second hours after administration (Chart 1). In the majority of animals the level of the conjugated form of PABA exceeded 2 or 3 times the concentration of free PABA. This applies to the "Amphojel" series where the values ranged between 3 to 10 mg. per cent (conjugated) and 1 to 4 mg. per cent for the free PABA (or DS). No appreciable differences were found at the end of the four hours period when an increase of the free acid was noted. It is of interest to note that in some guinea pigs of the "Amphojel"

series a significant rise in free PABA values up to 8 mg. per cent was observed 11 hours after the last dosage of the drug was given. In these cases the free PABA levels exceeded those of the conjugated values.

As compared with these observations guinea pigs similarly treated with the soluble NaPAB exhibited an occasional exceedingly high value for free PABA (69 mg. per cent) at the end of the first hour after the intake. This was followed by a rapid decline during the next three hours, however, at the end of the eleven hour interval without further drug supply a definite increase of free PABA level occurred. At this time only traces of conjugated PABA were detected (Chart 1).

It was thought that an increase of the molecular size of PABA in using its derivatives of less solubility may lead to a longer persistence of the drug in the body. For this purpose N-(p-aminobenzoyl) dl-phenylalanine (prepared at our request by Merck Co., Inc.) and thioglycolyl-p-aminobenzoic acid (kindly supplied by Endo Products, Inc.) were tried.

The first mentioned compound was given orally (0.45 gm. 3 times daily to each guinea pig) supplemented with subcutaneous injections (0.06 gm. 2 times a day). The treatment began 24 hours prior to the infection with spotted fever and was continued for the following four days. The response of the test guinea pigs was in no way different from that of the spotted fever control series.

The thioglycolyl-para-aminobenzoic acid was administered in 10 per cent solution in 4 per cent sodium bicarbonate, 3 cc. once a day, the total daily intake being 1.0 gm. The results were unsatisfactory: the test guinea pigs developed typical spotted fever and none survived.

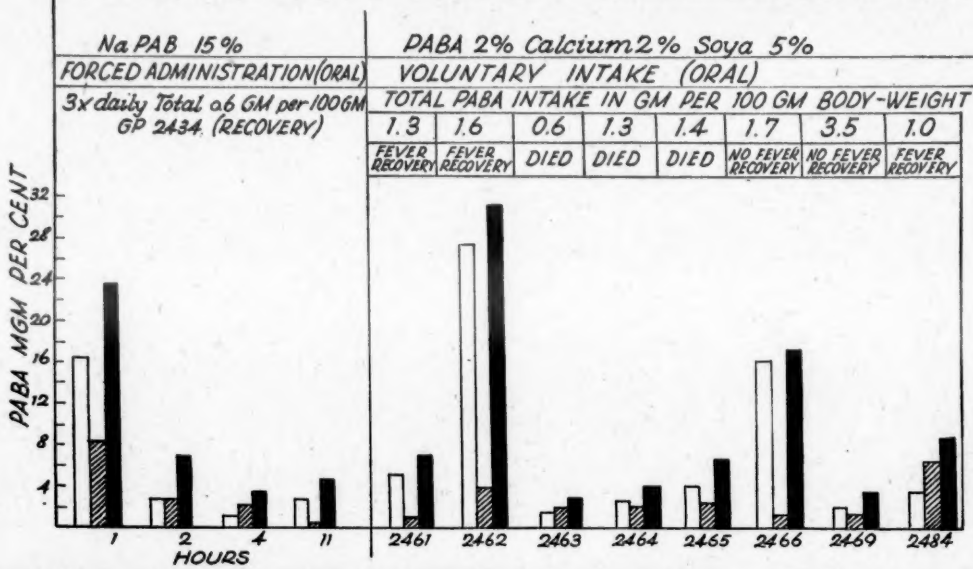
These results although negative are instructive as they show that an alteration in the molecular structure of PABA apparently nullifies its specific action on rickettsiae. This corroborates previous experience with other derivatives of PABA by Hamilton (1945).

b. Voluntary Intake of PABA.

The rapid rise and fall of PABA levels in the blood of guinea pigs treated by compulsory feeding were indicative of the

1.

PABA VALUES, FREE AND CONJUGATED, IN BLOOD OF GUINEA-PIGS INFECTED WITH SPOTTED FEVER & TREATED WITH PABA



transient presence of the drug in the circulation. This led to the comparison with the voluntary intake of the drug by the guinea pig. This previously used method was supplemented in the present study by measurement of the actual intake of the drug and by determination of PABA levels in the blood (Chart 1).

Several modifications of the drug containing ration were introduced, particularly as to protein and calcium content. The additional protein supply in casein or soya flour was introduced owing to the finding of a serious depletion in plasma protein in spotted fever patients. (Harrell, Venning and Wolff, 1944). The addition of calcium gluconate was suggested by the hypocalcemia in typhus patients as noted by Van Meerendonk (1942). When typhus patients were treated with calcium gluconate no fatalities were recorded by this author.

The analysis of the "casein series" of six guinea pigs shows in spite of an adequate intake of PABA (0.9–1.7 gm. per 100 gm. body weight) low PABA values not exceeding 2 mg. per cent. Only one of the test animals developed typical spotted fever while the fever reaction of the others was relatively low and of short duration. However, there were no survivals. Casein was then removed and calcium gluconate was added to the diet containing 2 per cent PABA. The total intake of PABA was from 1.3–1.7 gm. per 100 gm. body weight. One hour after initial feeding free PABA was found as high as 28 mg. per cent with the conjugated PABA not exceeding 4 mg. per cent. There were 50 per cent recoveries; one animal remained afebrile.

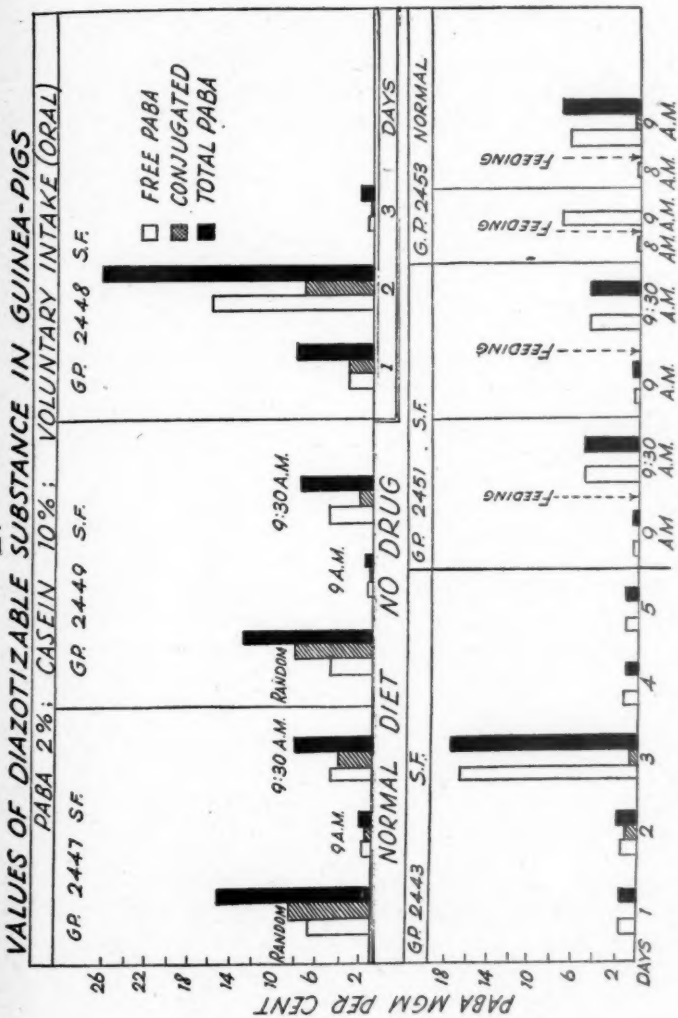
So far the combination of PABA, soya flour as source of protein and with the addition of calcium gluconate shows encouraging results. Of six guinea pigs of this series only one developed spotted fever and died, while the remaining five either exhibited abortive fever attacks of one day duration or remained afebrile. Attempts are being made in various lines to establish such balance of adjuvants which will possibly cope with the themical depletion of the infected host and perhaps permit a reduced PABA intake.

A Diazotizable Substance Found in the Blood of Normal Guinea Pigs

The numerous determinations of PABA values in the blood of guinea pigs displayed a wide range even under conditions of standardized dosage. While the character of the curve is mainly influenced by the time factor, it also is affected by the individual differences among guinea pigs, thus adding to the fluctuation of the PABA levels. Most probably the various phases of metabolic processes during which blood samples are taken may have a bearing on the results.

Since it is known that numerous substances (arsenicals, amino acids, adrenaline, etc.) may interfere with determination of PABA or give a coupling color reaction (Maher and Camp, 1939) control tests were made on normal guinea pigs. The purpose of this inquiry was to determine whether a diazotizable substance is present in the blood of untreated normal or spotted fever guinea pigs.

Similar to the PABA determination procedure, the first blood samples were taken early in the morning before feeding and then 30 minutes to one hour after the guinea pigs were fed with cabbage (or lettuce) carrots and oats. While hardly detectable traces of DS were found in fasting guinea pigs, a high value of a substance giving a color matching that of PABA (purple) was detected at the end of one-half to one hour after feeding (Chart 2). The readings were four to eight mg. per cent of the free substance which otherwise could be interpreted as PABA. Other blood samples were taken at random during the day and values ranging between 2 and 5.5 mg. per cent were found. In one guinea pig infected with spotted fever but untreated with PABA the DS level was as high as 16 mg. per cent (Chart 2). There was no appreciable increase of diazotizable substance after the samples were boiled with HCl for one hour. Consequently, the DTS did not appear in conjugated form, as contrasted with guinea pigs fed with PABA. Whatever the significance of this phenomenon, whether it is peculiar to some constituents of the diet or to the release of some specific endogenous substances, it affords a broader aspect to the values usually expressed as PABA.


2.
VALUES OF DIAZOTIZABLE SUBSTANCE IN GUINEA-PIGS
PABA 2%; CASEIN 10%; VOLUNTARY INTAKE (ORAL)
GP. 2447 S.F.
GP. 2449 S.F.
GP. 2448 S.F.
FREE PABA
CONJUGATED
TOTAL PABA
RANDOM
9A.M.
9:30 A.M.
RANDOM
9A.M.
9:30 A.M.
1
2
3
DAYS
NORMAL DIET
NO DRUG
GP. 2443
S.F.
GP. 2451 . S.F.
G.P. 2453 NORMAL
FEEDING
FEEDING
FEEDING
9 AM
9:30 A.M.
9 A.M.
9:30 A.M.
8 9 AM. A.M.
8 9 A.M. A.M.
PABA MGM PER CENT
DAYS 1 2 3 4 5

General Considerations

The introduction of p-aminobenzoic acid in the chemotherapy of rickettsial infections seems to have opened the gate to the heretofore inaccessible intracellular rickettsiae.

This new approach has also opened a wide field for speculative theories as to the mode of PABA action on the rickettsiae. While the possibility of direct action of PABA on the pathogenic agent is remote, there are indications that its suppressive effect is indirect through a complex mechanism in which the enzyme system of the host and the metabolic requirements of the parasite are involved.

In the light of these considerations an attempt was made in this study to investigate the correlation between the mode of administration of the drug, its concentration in the blood of the infected host and the course of the infection.

If the concentration in the system is a measure of its potential activity then the high PABA values registered should have been effective regardless of the mode of administration. Significant differences have been found in this regard since the compulsory supply of the drug in dosage causing free PABA levels as high as 43 mg. per cent by injection and reaching 69 mg. per cent by compulsory oral administration had with few exceptions no effect on the course and issue of the disease.

On the other hand, natural feeding which provided an intake of the drug at frequent intervals or possibly an almost constant supply of PABA in small doses corroborated previous results in experimental spotted fever (Anigstein and Bader, 1945). Under these conditions a total intake of 1.7 gm. of PABA per 100 gm. body weight over a period of seven days was found effective, particularly when protein (soya) and calcium were added (Chart 1). Our experience in using casein as a source of protein was strikingly unsuccessful, possibly as a result of detrimental conjugation of PABA with casein.

In the course of the analysis of blood plasma of normal and spotted fever guinea pigs not treated with any drugs, the presence of a substance was revealed which when diazotized and coupled gave a color reaction matching that of PABA. While this substance (DS) appeared only in traces in the plasma of

fasting guinea pigs, its level rose unexpectedly and immediately after the intake of normal diet (Chart 2). No evidence of its conjugated form in the normal series of guinea pigs could be disclosed. Although the nature and the source of this substance are still unknown, its presence under normal conditions deserves attention in evaluating PABA levels.

ACKNOWLEDGMENTS

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The chemical aspect of the problem derived great benefit from the authoritative suggestions of Dr. E. H. Frieden.

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PATHOGENICITY OF THE ASPERGILLI OF OTOMYCOSIS*

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Certain fungi are found associated with the clinical condition known as "otomycosis." They are presumed in a general way to play a pathogenic role. The present study contemplates a critical appraisal of their pathogenicity.

Otomycosis consists in a lesion of the external ear canal with the clinical signs of an exfoliative dermatitis and a tendency to exhibit fungus growth. In the most aggravated form of the disease, exfoliated epithelium soaks up discharged fluids to form a wad of sodden matter that resembles macerated paper pulp. A plug of this exudate fills and obstructs the depths of the canal.

In this pronounced form of the disease, certain fungi are ordinarily present in the exudate. They occur so prolifically that their mycelia can be seen microscopically to weave through the epithelial debris. Here and there appear the fruiting structures characteristic of their genus. In some instances the plug of exudate is visibly moldy and covered with mold spores. By cultural methods these fungi may be isolated and identified.

In a series studied by us, twelve cases had been described by medical attendants as presenting this thick and characteristic exudate. These twelve yielded culture of the *Aspergillus niger* in 5 instances, of *A. flavus* in 3, of both these species in one, of a species of scopulariopsis in one, and no fungus at all in two. In a previous paper (Sharp, John and Robison[10]) we described more fully the findings on this series of cases. The cultures were obtained by planting the specimen of exudate to the surface of Sabouraud's agar and incubating at room temperature.

The same characteristic flora has been reported by investigators of the condition in other parts of the world. In most

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localities where the condition prevails, *A. niger*, *A. flavus* or both of these fungi have been recovered, and now and then other incidental fungi as well. This is the mycologic finding with which we will be concerned in this paper.

In a majority of cases, exfoliative lesions of the canal are less pronounced than this and fail to produce this thick exudate. Such of these milder lesions as occurred in our series did not exhibit any significant mycology. While clinicians often regard them as being of the same essential nature and etiology, their mycotic character has not been demonstrated. Of an equivalent number of cases described to us as not having the typical appearance noted above, with characteristic thick exudate, none gave positive results when cultured or examined microscopically for fungi.

The bulk of the cases submitted to us were not so described as to indicate severity of lesion or nature of exudate. These cases yielded fungus growth in smaller proportion than the twelve first mentioned, but such positive cultures as were obtained represented the same general flora. A mixture of typically discharging cases having positive findings and of the milder cases having negative findings could well have afforded these results for the entire series.

Presence of the organisms mentioned does not, of course, indicate their pathogenicity. Whether these fungi subsist in the lesion saprophytically or parasitically has long been a subject of contention. In some instances this mycologic growth appears as a complication of discharging otitis media, either acute or chronic. In this case the organisms are not the primary invaders, at all events. They are found multiplying in the suppurative matter and it appears as if they are peculiarly suited to such conditions of growth. Chisholm and Sutton[2] state that the development of otomycosis requires prior pathologic conditions involving maceration of the tissue.

The two species of aspergillus commonly found in otomycosis are well known saprophytes, as are the other fungi occasionally found present. They often give trouble as contaminants. Various organic substances are prone to develop a growth of these organisms if exposed to the dust of the air. They both abound on the normal human skin, though with

nothing like the frequency that they do in the ear discharge (Minchew, Collins and Harris[7]).

Some of our dermatologic diagnostic tests afforded data on the relative frequency with which these particular species of mold occur on the body surface as compared with other species. We identified all fungi that came up in cultures of epithelial scales or hairs from ringworm cases. The enumeration of these saprophytic contaminants gives a rough picture of the common fungus flora of the human skin and hair. Prime objectives of these tests had to do with dermatophytes, with which we are not here concerned.

The saprophytic flora of the skin, as determined in this manner, proved to include numerous species of fungus falling in 26 genera. Presumably, the auditory canal is exposed to the spores of these same molds. The flora in otomycosis is not an indiscriminate sample of them however. Only a certain few of the saprophytes that ordinarily contaminate the skin occur with any frequency in otomycosis discharges. The few that do occur in otomycosis are not the fungi most prevalent on the skin; the latter did not occur at all in the exudate of our cases.

Of all fungi to which the body is exposed, the only species obtained in our otomycosis cases were *A. niger*, *A. flavus*, and rarely a species of scopulariopsis, as already noted. These fungi did find a prominent place among the skin contaminants. The *A. niger* occurred with about twice the frequency of *A. flavus*, a ratio similar to that in the ear discharge. But of all the species of aspergillus represented in the skin flora, only these two occurred in the otomycosis cases. Additional species were found on the skin, and one of them, *A. versicolor*, more frequently than either of these two.

A selective factor in otomycosis evidently favors these particular fungi over others. The identified isolations we made from the skin numbered considerably over a thousand, and these included only 97 instances of *A. niger*, 40 of *A. flavus*, and 17 of scopulariopsis. Isolations of other species which did not occur in otomycosis specimens numbered 972.

It becomes evident that very few of the numerous assortment of fungi to which the body surface is exposed may proliferate in the exudate of otomycosis. Others of this assortment

have been described by various authors as being incidentally present. This also is our experience. But these latter do not proliferate in the discharge sufficiently well to appear microscopically. Their development in culture indicates only that their spores are present in the ear, just as they are on the skin elsewhere.

The nature of the selective factor is not as yet evident. Special adaptability of these few fungi to a medium of tissue detritus suggests itself as a possibility, or adaptability to the pH of such matter perhaps. These possibilities might be explored. Why these two species of aspergillus should exhibit nutritive predilections unlike the others is not at once apparent. Under ordinary cultivation they and the other molds of the skin flora exhibit much the same growth requirements.

If this nutritive predilection were the determining factor, it would follow that the organisms play little part in the inflammation beyond growth in its exudate. They might be considered borderline pathogens, as they help form the plug that closes the auditory canal and interferes with hearing. Whether this mechanical impairment of function is sufficient effect to constitute pathogenesis, as Bristow[1] suggests, is a matter of definition.

Many observers have gained the impression that the organisms exert a more decisively pathogenic effect. Selective harboring of these organisms could result from toxic capacities they might have for the tissue involved. Or again, a susceptibility of that tissue to invasion by these particular fungi would lead to their prevalence.

Some otologists are convinced by their clinical observation, together with such evidence as finds mention above, that the fungi in the otomycosis lesion are definite pathogens. These clinicians usually conceive of the condition as an outright infection by the fungi found present (Gill,[3] Whalen,[12] et al.). This view is based largely on therapeutic evidence. The condition yields to local applications containing fungicidal medication.

Such evidence would be more generally convincing if the applications employed had no activity other than the fungicidal. A number of fungicidal preparations have been em-

ployed with success, but their therapeutic effectiveness is not limited to the mere killing of fungi. To the extent that they might react beneficially regardless of mycotic involvement, they fail to bear on the question of pathogenicity.

The nature of the condition is such that direct test of pathogenicity would be difficult to apply. Since the disease does not ordinarily develop in the normal canal but only in the presence of prior discharge or other abnormality, an infection of healthy tissue could hardly follow its exposure to the spores anyway. From spores planted to a discharging tissue, on the other hand, any mycelial growth that took place could well be saprophytic; development of the otomycosis picture would give little indication as to infectivity.

The recognized distribution of otomycosis hardly suggests the infectivity of these fungi as probable cause. The very limited occurrence of the disease in the face of widespread exposure to the spores rather argues against it. In contrast with the extremely wide habitat of these particular fungi, otomycosis is of very limited geographic distribution (Trexler[11]). In localities where cases are encountered, the latter are few in number as compared with great abundance of the spores in the air. With all due allowance for the natural resistance exhibited by persons who have normal ears, one might think that a pathogenic organisms so very widely distributed would lead to greater prevalence of the disease.

This brings us to consider whether the fungi that occur in the lesion are identical in pathogenicity with strains of the same species that lead a saprophytic existence all about us. Peculiarly virulent strains might be infective, even though the usual members of the species are not. The occurrence of such strains could explain the geographic concentrations of the disease just mentioned, though climatic factors have a more apparent influence.

There has been a suggestion at times of epidemic incidence such as might result from extraordinarily virulent strains being at large, though the evidence is not at all convincing. Gordon[4] reported an outbreak in the Canal Zone. We encountered a run of 17 cases during October and November of one year, whereas we rarely see more than a few cases

per month. Neither of these flare-ups were associated with one species of fungus however, and it is not easy to think of unusually virulent strains of both *A. niger* and *A. flavus* arising simultaneously. Besides, the number of cases was not great enough to rule out chance incidence fluctuations.

We explored this question as to the existence of peculiarly pathogenic varieties of aspergillus by means of cultures we had isolated. We compared strains of *A. niger* recovered from the exudate in otomycosis with other strains from the skin. We did the same with strains of *A. flavus*.

From one series of experiments we sought to learn whether strains found in otomycosis had greater toxicity than strains found existing harmlessly on the skin. Various toxic properties have been described for these and other aspergilli, though none of them have been shown to take part in the inflammation. The presence exclusively in otomycosis strains of any toxic substance might be regarded as indicative of pathogenicity.

We obtained extracts of *A. niger* and *A. flavus* which on repeated inoculation into rabbits proved often to have toxic effect. These were the extracts separated by means of 10 per cent sodium chloride, to have mention presently. In its action, this toxic substance resembled one separated from aspergilli in a different manner by Henrici[5]. As a rule the animals continued in perfect health during three inoculations at several days' interval and a subsequent rest period of two weeks. They then succumbed to the next inoculation and died in from four to seven days.

Death occurred with characteristic pathologic effect. The conspicuous autopsy findings consisted in a profuse effusion into body cavities, variable engorgement of the mesentery, hemorrhagic and other changes in the lungs, and necrotic or other changes in the liver. These morbid changes were recent in nature and lacked evidences of the repair that would accompany a slow, cumulative effect of all toxin given. They suggest an initial tissue sensitization, such that later inoculation caused rapid intoxication.

Using *A. flavus*, we compared the toxicity of strains recovered from the discharge of otomycosis with that of strains recovered from the air or normal skin. Of four animals given

the extract from otomycosis strains, two died characteristically from the toxin and two survived the five inocluations administered. Two animals given the extract from air or skin isolation strains both died from the toxin. Additional animals in both groups died from anaphylactic shock, and afford no evidence as to toxicity. While the organisms' protoplasm did prove to contain toxic substance, we did not find reason to suspect a greater pathogenicity in the otomycosis group dependent on that property.

We directed our consideration also to the possibility of peculiarly invasive strains finding place within these species of aspergillus. A familiar situation among the bacteria is that in which ordinarily harmless species include one or more infective types. This method of approach did not seem especially promising among the fungi but was not without possibilities.

Serologic differentiations are not as clean cut as among the bacteria (Sharp[9]). Antigenic relationships tend to be much broader, such that a serologic group may cover the entire species of fungus, or even more than one species. Reactions within this range are often irregular and erratic.

Experiments were devised to show whether serologic groups existed among the strains we had obtained of *A. niger* or *A. flavus*, and if so whether otomycosis strains typed together. Significant findings would consist in otomycosis strains cross reacting with each other to higher titer than with saprophytic strains from other source. In serologic work with other kinds of mold, we had encountered conspicuously higher titered cross reaction between some strains than others.

The precipitin test was employed. Antigen preparation, animal immunization, and precipitin test routine followed procedures described in a previous report (Sharp[8]). The most potent antigen obtained was one extracted as described in that report with 10 per cent sodium chloride solution. We also employed a normal saline extract such as has commonly been used by others in serologic study of molds (Link and Wilcox[6]). Since different antigen fractions might well differ in type definition, it seemed well to use more than one preparation.

Experiments were made separately for *A. flavus* and *A. niger* strains. No cross precipitation took place between strains of the one species and those of the other. When the more potent antigen was employed, all strains of either species cross reacted strongly among themselves. With the weaker antigen, practically all strains of either species cross reacted to some degree.

Reactions obtained with *A. flavus* strains are presented in Table I. The antiserums immune to otomycosis strains reacted

TABLE I

Precipitin Tests with Aspergillus Flavus Strains.

	Antiserums from EAR Isolations (Otomycosis).																	
Antigens: EAR isolations		611			1624			Antigens: AIR isolations		611			1624		
	611	+	+	+	+	+			1837	+	+	+	+	+	
	1624	+	+	+	+	+	+		166B	+	+	+	+	+	+
	x	+	+	+	+	+	+		1261	+	+	+	+	+	+
	1788	+	+	+	+	+	+		814B	+	+	+	+	+	
	1822	+	+	+	+	+	+		1740A	+	+	+	+	+	+
									1755A	+	+	+	+	+	+
									449	+	+	+	+	+	+

in the same average degree with the antigens of air isolation strains as with a series of otomycosis strains. For these tests we employed antigen extracted with 10 per cent sodium chloride solution and the reactions in most instances were pronounced.

For the greater number of our serologic reactions with *A. niger* strains we employed as antigen a normal saline extract. It seemed possible that a better differential antigen fraction might be separated by this other extraction method. This preparation did not immunize animals as highly nor as uniformly as that first described. Among certain groups of fungi we have noted that high titer reactions distinguish less clearly than those of lower titer. Where cross reactions of low titered antiserums relate certain members of a group, those of more highly immunized serums may relate in similar degree the entire group. This has been observed by others also (Link and Wilcox[6]).

We made our extractions in the manner mentioned above except for the lesser strength of extractive saline. In order to concentrate the protein into effective immunizing strength we salted it out as before. We used the same procedure of animal inoculation. The antiserums of animals immunized with these antigens varied widely in the immune titer attained. All exhibited lower titer than antisera produced with the antigen first described.

Two rabbits immunized with otomycosis strains and one with an air isolation strain developed hardly any immunity at all. Nearly all cross reaction tests with these three antiserums were negative and the few positive tests were of low titer. A fourth serum, immunized with an air isolation strain, gave weakly positive reactions (+ or ±) about as often as it did negative. All of these weakly positive cross reactions were scattered indiscriminately, and without regard to the source of isolation of the strain.

Eight antiserums in all were prepared by antigens extracted with normal saline, all from *A. niger* strains. There were the four just mentioned and four others. The remaining four antiserums attained immunity of somewhat higher degree than those just described.

Two antiserums immunized with otomycosis strains (Table II) reacted with most of the antigens against which they were tested, though never to a pronounced degree. Positive reaction

TABLE II

Precipitin Tests with Aspergillus Niger Strains.

	Antiserums from EAR Isolations (Otomycosis).					
Antigens: EAR isolations		1489	1469	Antigens: AIR isolations	1489	1469
	1489	+ +	+	233A	+	+ +
	1469	+	+ +	1807	±	+
	1789	+	+	1779	0	0
	1787	+ +	+	824	±	0
	1817	0	0	1821	+	+
	1824	±	+	1799	+	+
	1758	+	±	1811A	+	+
	1641	+	+ +	1808	+	+
	1822	±	±			
	1457	+				

occurred about as frequently with air isolation strains as with other otomycosis strains. The strongest reaction, the average reaction, or a failure to react at all appears about as frequently with strains from the one source as from the other.

Two antiserums were immunized with strains recovered from dust or skin. As it happened, these reacted more strongly (Table III). The strains tested against these two antiserums

TABLE III

Precipitin Tests with Aspergillus Niger Strains.

	Antiserums from AIR Isolations (Dust; Skin).															
Antigens: AIR isolations		1807			1821			Antigens: EAR isolations		1807			1821		
	233A	+	+		+	+	+		1489	+	+		+	+	+
	1807	+	+	+	+	+	+		1469	+	+	+	+	+	+
	1779	+	+		+				1789	+	+			0	
	824	+	+		+	+			1787	+	+	+		0	
	1821	+	+	+	+	+	+		1817	+	+		+		
	1799	+	+			0			1824	+	+		+	+	
	1811A	+	+	+	+	+			1758	+	+		+	+	
	1808	+			+	+			1641	+			+	+	
									1822	+	+		+	+	
									1457	+	+	+	+	+	

usually gave a definitely positive though not pronounced reaction. Occasionally the reaction was pronounced and occasionally weak or negative. In both instances these antiserums reacted to the same average degree with otomycosis strains as with air isolation strains.

We also prepared from *A. niger* strains the more potent antigen described above, and antiserum. A small series of cross tests gave results essentially like those obtained with *A. flavus* strains, as shown in the first table.

So far as these two preparations of antigen can discriminate, it apears that otomycosis strains are not a more closely related group than unselected strains of the species as a whole, whether of *A. niger* or *A. flavus*. Such cross reactions as were obtained fell indiscriminately and without regard to the source of isolation of the strain.

In summary, it may be said that while these two species of aspergillus are closely associated with otomycosis, there is not adequate evidence to establish for them an infective or toxic role in the inflammation.

Conclusions

1. The fungi associated with otomycosis are of common saprophytic species that abound on the normal skin and in the dust of the air.

2. The lesion does not harbor indiscriminately all fungi to which the body is exposed, but favors *A. niger*, *A. flavus* and occasional others. We did not learn the nature of the selective factor.

3. We found little reason to think that a susceptibility of the tissue to attack by these particular fungi was what accounted for their thriving so well in the lesion.

4. Strains of these fungi which were associated with the disease failed to show properties unshared by other strains of the same species. Otomycosis strains did not form a more toxic group, nor a group distinguishable from other strains of the species by antigenic characteristics.

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COEXISTENCE OF THE ANTIBODIES OF YELLOW FEVER AND WEIL'S DISEASE IN HUMAN SERUM*

A. Packchanian and T. G. Price

The clinical differentiation between yellow fever and Weil's disease is difficult. For this reason, erroneous diagnoses have been made, particularly in the past, when the laboratory methods of diagnosis of these diseases were not fully developed.

It is impossible to estimate in how many instances these two diseases have been mistaken one for the other. The last epidemic of yellow fever in the United States occurred in New Orleans in 1905. Dr. Stimson, then of the National Institute of Health, noted in the tissues of one of the fatal cases, who presumably died of yellow fever, an organism which he called (*? Spirochaeta* interrogans Stimson, 9). In 1937 Dr. Stimson gave an original slide of this case to one of the writers (A. P.) for study; examination of this preparation revealed many spirochaetes which are morphologically indistinguishable from *Leptospira icterohaemorrhagiae*. It is concluded that in this particular case Weil's disease existed alone or concomitantly with yellow fever. The same conclusion was reached independently by Sellards (Sellards, 8). In 1918 in South America 27 cases, presumably of yellow fever, were referred to Noguchi for further study (Noguchi, 1). He succeeded in isolating *Leptospira* from six cases and concluded erroneously that yellow fever was caused by *Leptospira*. Here again Weil's disease apparently either was mistaken for yellow fever or the two diseases coexisted. Besides these two classical examples in which Weil's disease was confused with yellow fever, many other instances of erroneous or incomplete diagnoses have occurred in the past (Sawyer, 5; Strong, 10).

The object of the present study is to determine whether or not patients who have recovered from jungle yellow fever and have demonstrable antibodies for the virus of yellow fever also have antibodies for *Leptospira icterohaemorrhagiae*.

*From the Microbiology Laboratory, The University of Texas Medical Branch, Galveston. Submitted for publication June 4, 1946.

Methods and Materials

Samples of blood serum were collected by the Rockefeller Foundation during 1939 from 94 persons who had recovered from sylvatic or jungle yellow fever. They were taken at widely varying and, in most cases, completely unknown intervals of time after being sick with yellow fever. All of the specimens gave a positive mouse protection test for yellow fever by the intraperitoneal mouse inoculation method (Theiler, 11) These results were obtained before the samples were sent to one of the writers (A. P.) during 1939 through the courtesy of Drs. W. A. Sawyer, F. L. Soper and J. A. Kerr.

The antibodies of Weil's disease were determined by a microscopic agglutination test, using Type I *Leptospira icterohaemorrhagiae* (Schuffner, 6, 7; Packchanian, 2).

Experimental Data

Out of 94 samples of serum having a positive mouse protection test for yellow fever, six showed positive agglutination reactions with Type I *Leptospira icterohaemorrhagiae.* The agglutination titer of the positive sera ranged from 1:100 to 1:1,000. The reactions were prompt and complete within two hours.

Discussion

The presence in blood serum of the antibodies of either of these diseases makes possible only a retrospective diagnosis. However, a rise in agglutination titer is usually indicative of an acute or recent attack of Weil's disease (although the possibility of such rise being due to an anamnestic reaction cannot entirely be eliminated). For the diagnosis of active cases of Weil's disease by serological means a rise in the agglutination titer during an interval of two or three weeks is necessary. However, for absolute diagnosis of Weil's disease it is essential to isolate *Leptospira icterohaemorrhagiae* from the patient's blood or urine by cultural or animal inoculation procedures and, whenever possible, to demonstrate the *Leptospira* in the blood or tissues of fatal cases (Packchanian, 2).

It must be borne in mind that, at the present time, at least four serological types of *Leptospira* are known to exist (2); however, only Type I *Leptospira* was used in this study.

For the absolute diagnosis of a case of yellow fever in the early stage of the disease, it is necessary to inoculate two groups of white mice *(Mus musculus)* with blood from the patient suspected of having yellow fever. One of the groups of mice should be inoculated immediately with yellow fever immune serum and serves as a control. After 10 days, if the control group survives and the group receiving no immune serum dies with no evidence of bacterial injection, the diagnosis is active yellow fever. A diagnosis of yellow fever in a convalescent or a recoverd patient is made by the mouse protection test, in which the mouse is protected from active yellow fever virus by the antibodies in the patient's serum. In the fatal cases the diagnosis of yellow fever may be established by the typical pathology found in the liver.

Since the antibodies of both diseases remain in the blood for an indefinite time (Sawyer, 5; Strong, 10; Packchanian, 3; Sawyer, 4), finding evidence of one of these diseases does not exclude the presence of the other disease.

Summary

Serum samples from a number of persons who had antibodies against yellow fever due to attacks of sylvatic or jungle yellow fever were received from Brazil and tested for antibodies for Weil's disease by microscopic agglutination tests against Type I *Leptospira icterohaemorrhaegiae.* Out of 94 persons whose serum gave a positive mouse protection test for yellow fever the serum of six had a diagnostic titer of the antibodies for Weil's disease. The agglutination titer ranged from 1:100 to 1:1,000 and the reaction was prompt and complete within two hours.

The presence of antibodies of both of these diseases in the serum of six of the patients made possible retrospective diagnoses and indicated that these six patients contracted Weil's disease at the time of, before, or after the attacks of yellow fever.

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PHYSIOLOGICAL RESPONSES OF ADOLESCENTS TO EXERCISE

NATHAN W. SHOCK*[1]

Measurements of physiological functions under standardized basal conditions provide essential data for the study of changes with growth and maturation. However, the measurement of the ability of the organism to compensate the physiological displacements induced by stress or strain offers the only way of assessing the reserve capacities of the organism. For a satisfactory study of developmental physiology, it is obviously necessary to include some measurements which will attempt to measure age differences in such reserve capacities. For this purpose, maximal physical exertion was selected as a physiological stress which could be applied safely in the study of adolescents. As an index of adjustive capacity, the extent of displacement and the rate of recovery of certain physiological functions such as respiration, pulse rate, blood pressure, ogygen uptake, and carbon dioxide elimination were studied in a group of 100 children following a short period of intense exertion. Tests, under standardized conditions were made on the same children at 6–12 month intervals over the age span of 13.0–18.0 years. This paper is a preliminary report of a general survey of some of the results obtained. Details of the results await further statistical analysis of the experimental data.

Experimental

Subjects: The subjects studied were 100 children from the University of California adolescent study previously described

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[1]The experimental work reported was carried out by Dr. Shock while Assistant Professor of Physiology and Research Associate, Institute of Child Welfare, University of California, Berkeley.

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(3). In addition, tests for comparative purposes were made on coöperative staff members, college students and pre-adolescent children from other growth studies being carried on at the Institute of Child Welfare.

Experimental: Following the determinations of blood pressure, pulse rate, and oxygen uptake under basal conditions as previously described (8), a Siebe-Gorman halfmask, fitted with inspiratory and expiratory valves, was securely tied over the face of the subject, and connected to a Douglas bag carried on the subject's back. Each subject then ran up 5 flights of stairs (a height of 17.7 m.). At the top of the stairs, the subject lay down on a cot, the inspiratory tube was attached to a source of outdoor air, and the expiratory tube was attached to a recording system which collected the expired air. This apparatus (Figure 1) consisted essentially of two pairs of Tissot spirometers. The small spirometers, which held 9.19 liters of air, were used to collect continuously the expired air during the early stages of recovery while the large spirometers, which held approximately 50 liters, were used during the later stages of recovery. Samples of air were drawn from each spirometer as filled, into gas sampling tubes over mercury and were analyzed for CO_2 and O_2 content with a 10.0 cc. Haldane apparatus. The two small spirometers were fitted with a valve which automatically shifted the input to the second spirometer when the first was filled, and at the same time operated a marker on a paper polygraph. Thus the volume of expired air was calculated from the time required to expire 9.19 liters of air.[2]

As soon as the subject lay down, a sphygmomanometer recording system (10) and inflated to 40 mm. Hg. This provided a continuous record of each heart beat on the paper polygraph. One observer immediately began recording systolic and diastolic blood pressures with a sphygmomanometer cuff previously attached to the right arm of the subject. A large telechron clock at the side of the manometer enabled the

[2]This apparatus is described in detail elsewhere (10). For later experiments, the apparatus was altered somewhat to provide for continuous automatic sampling of the expired air. A more detailed report on this apparatus is in preparation.

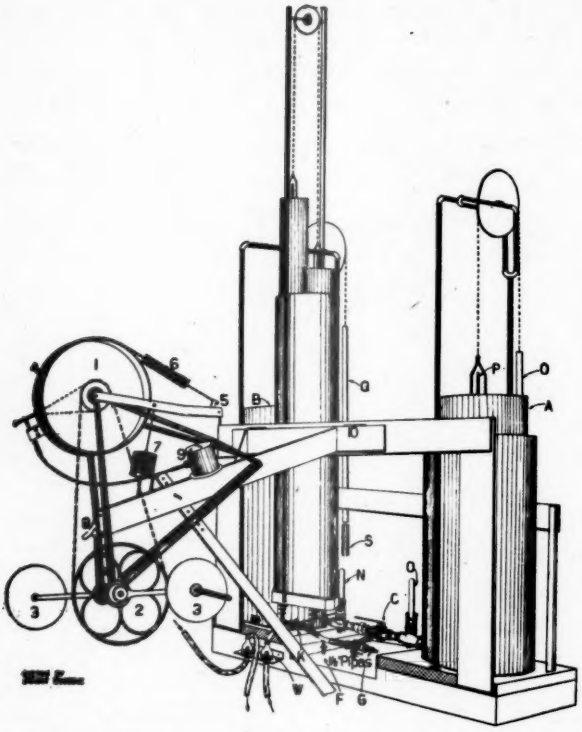

Figure 1. Bicycle ergometer in position for arm exercise with subject lying supine. Spirometers for automatic collection measurement of volume and sampling of all air expired by the subject are also shown. When stair climbing was used as exercise, the ergometer, hinged at 10, was swung upward out of the way. For complete description and calibration see reference 10.

operator to read blood pressures at exactly 30-second intervals. After the first 5 minutes, blood pressure was recorded at 1-minute intervals. A record of the actual time the blood pressure reading was made was provided by a marker on the paper polygraph actuated by a foot switch controlled by the operator. All blood pressure readings were called out by the operator as made and recorded by another assistant. The time of the exercise was automatically recorded on the polygraph by

switches provided at the bottom and top of the stairs. Measurements were made for 30–60 minutes after the exercise. With the younger children, restlessness was minimized by projecting moving pictures (travelogues) on the ceiling of the darkened experimental room.

For comparative purposes, arm exercise was substituted for stair climbing in some experiments. For this purpose, a calibrated ergometer (Figure 1) was used (10). In these experiments, the subject performed the same amount of work with his arms (while lying down) as would have been required for climbing the stairs. The time of exercise in these experiments was 3 minutes. The same observations were made as in the stair-climbing experiments.

Treatment of the data: Cardiovascular measurements. From the polygraph records, pulse rate was estimated by counting the number of beats included in the interval of 10 seconds before and 10 seconds after the midpoint of time between the measurement of each systolic and diastolic blood pressure as shown on the polygraph record. This procedure made it possible to study relationships between simultaneous measurements of pulse rate and blood pressure during the course of recovery after exercise. The actual time of measurement of systolic and diastolic blood pressure was obtained from the polygraph record and entered on the data sheet opposite the appropriate blood pressure measurements.

From the time required to exhale 9.19 liters of air, the respiratory volume was calculated in liters per minute (reduced to 0° C. and 760 mm. Hg.).

From the respiratory volume and the O_2 and CO_2 content of the expired air, ozygen uptake and carbon dioxide elimination were calculated as cc. per kg. per minute for each collection period. In addition, all results (both metabolic and cardiovascular) were expressed as per cent of the basal values determined just prior to exercise.

The data thus obtained were plotted against time for each experiment to show recovery rates. Figures 2 and 3 illustrate sample curves obtained in a single child after stair climbing and bicycle exercise respectively. Such curves were drawn for

each test made at 6-month intervals on each of 100 children between the ages of 13.0 and 17.5 years (a total of over 900 charts). Since it was impossible to obtain measurements at exactly the same time in all experiments, interpolated values were read from the individual curves for each set of measurements at standard time intervals after the exercise, viz.: 1 min., 2 min., 5 min., 10 min., 20 min., and 30 min. The per cent deviation from the basal determinations of each child was then calculated for each type of measurement.[3] Average values

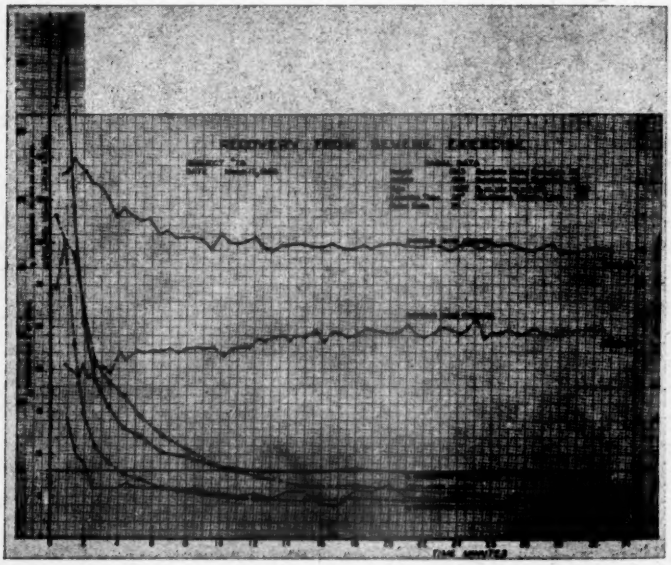

Figure 2. Recovery of physiological displacements produced by severe exercise. Sample experiment. Boy: aged 16.7 yrs.; ht. 171.3 cm.; wt. 53.0 kg. Exercise time—26 sec. ●——●——● systolic blood pressure, mm. Hg.; ——●—— ——●—— diastolic blood pressure, mm. Hg.; O—— – —— – ——O ventilation volume, liters per min.; O— — — —O oxygen uptake, cc. per kg. per min.; O————O oxygen uptake, per cent of basal oxygen consumption; ● —— ● ——● pulse rate, beats per min.

[3]Due to space limitations, only the results for one minute after exercise are discussed in the present report.

for all the children tested were calculated according to chronological age groups.[4]

Results

Recovery curves: Sample curves showing the displacement and recovery of physiological measurements following stair-climbing and arm exercise in an adolescent boy are shown in Figures 2 and 3, respectively. Examination of these curves shows that after stair-climbing (26 sec. of exercise) the systolicc blood pressure increased from 110 mm. to 175 mm. Hg. and the diastolic pressure dropped from 64 to 45 mm. Hg. Within 15 minutes after exercise the changes in blood pressure values became stabilized at levels slightly greater than basal. The pulse rate after exercise increased from 59 beats per minute to 120 per min. The period of rapid fall in pulse rate occurred

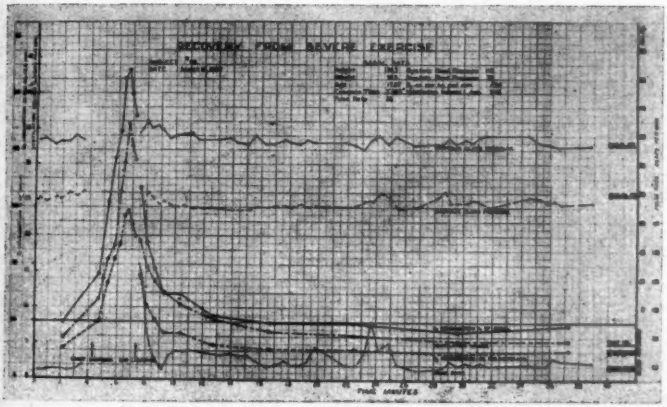

Figure 3. Recovery of physiological displacements produced by arm exercise with bicycle ergometer. Sample experiment. Boy: aged 17.7; ht. 174.3 cm.; wt. 57.5 kg. Exercise time—3′ 025″. ●——●——● systolic blood pressure, mm. Hg.; ——●—— ——●—— diastolic blood pressure, mm. Hg.; O—— – —— – ——O ventilation volume, liters per min.; O— — — — —O oxygen uptake, cc. per kg. per min.; O————O ozygen uptake, per cent of basal ozygen consumption; ● ——— ● ——— ● pulse rate, beats per min.

[4]Average values according to chronological ages were computed by including individuals between the ages of 14.26 and 14.75 in the 14.5 year age group. Thus 13.0; 13.5; 14.0, etc., represent the mid-point of each age category.

within 5–10 minutes after the exercise. The pulse rate remained elevated even after 30–35 minutes of rest. Respiratory volume increased from 5.74 liters per min. to 34.2 liters per min., and oxygen uptake increased from 4.62 cc. per kg. per min. to 35.0 cc. per kg. per min. after exercise. This increase in oxygen uptake was 750 per cent of the basal value. Recovery of the respiratory and metabolic displacement produced by exercise was very rapid—in this particular subject it was complete within 15 minutes after exercise. In the ergometer experiments with arm exercise, the physiological displacements were all in the same direction, but of somewhat less extent (Figure 3).

Age changes in cardiovascular adjustments after exercise: In general, the pulse rate fell rapidly during the first 5–10 minutes after exercise, but failed to reach basal levels within

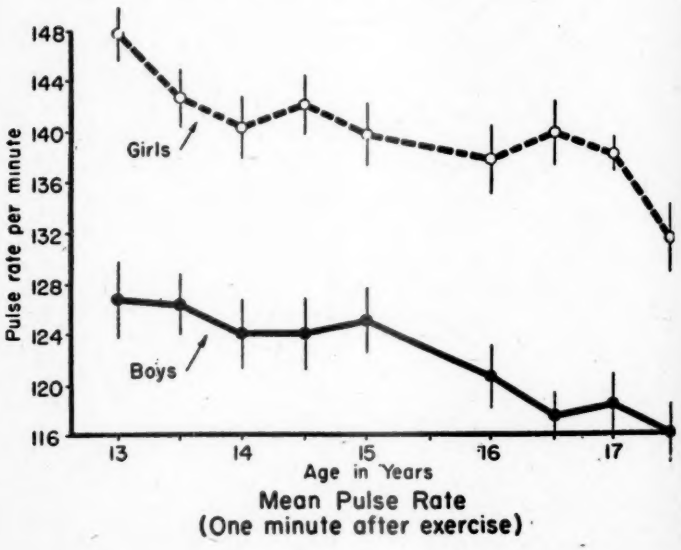

Figure 4. Age changes in pulse rate response to severe exercise. Average pulse rate one minute after exercise. The vertical line through each point indicates ± 1 standard error of the mean value. Male O——————O; Female O—— —— —— ——O. (From: National Society for the Study of Education, Part I, 43rd Yrbk., p. 66, 1944.)

30–45 minutes even in the youngest children tested. The average pulse rate one minute after the end of exercise at increasing chronological ages is shown in Figure 4. This figure shows that pulse rate was increased more in girls than in boys at all ages. In both sexes, the increase in pulse rate after exercise becomes less as children grow older. This reduced capacity to increase pulse rate seems to continue throughout adult life (5).

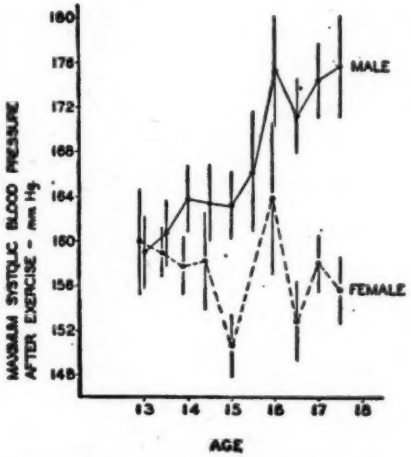

Figure 5. Age changes in blood pressure response to severe exercise. Average maximum systolic blood pressure observed after exercise, mm. Hg. O———O Males; O— — —O Females.

The average maximum systolic blood pressure after exercise increases in boys from 160 mm. Hg. at 13 years of age to 175 mm. Hg. at 17.5 years. In girls, the maximum pressure after exercise decreases from 160 mm. at age 13 years to 155 mm. at age 17.5 years (Figure 5). Thus at the age of 13, no difference in blood pressure response to exercise is observed between the two sexes, but with increasing maturity, the rise in pressure after exercise becomes much greater in boys than in girls. It was also found that as the children grew older,

there was a tendency for the systolic blood pressure to continue to rise for 1 to 2 minutes after cessation of the exercise. Thus the maximum reading for systolic pressure was obtained on the average 1.3 min. after the end of exercise in 13-year-old boys, while in 18-year-olds the maximum pressure reading was not obtained until 1.75 min. after the end of exercise. Thus there is evidence that the systolic pressure response to exercise takes place more rapidly in younger than in older children.

The changes in diastolic blood pressure are extremely interesting, but difficult to interpret. In the younger children, the diastolic pressure[5] drops to its minimum either during or following exercise. At the age of 13, the average time of this minimum in diastolic pressure was 5 minutes after the end of exercise in both girls and boys (Figure 6). With increasing

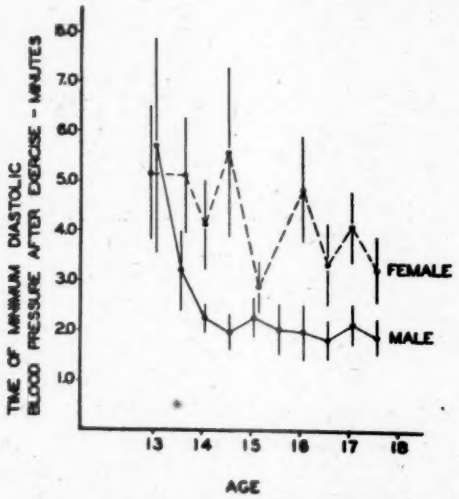

Figure 6. Age changes in average time after severe exercise, when diastolic blood pressure was lowest. O———O Males; O— — —O Females.

[5]In this report, the term "diastolic pressure" is used to denote the manometer reading observed at the 4th sound of Korotkow by the auscultatory method.

age the time at which the minimum pressure appeared decreased to 2 minutes in boys but remained higher in girls (average 3–4 minutes). Figure 7 shows that the average drop

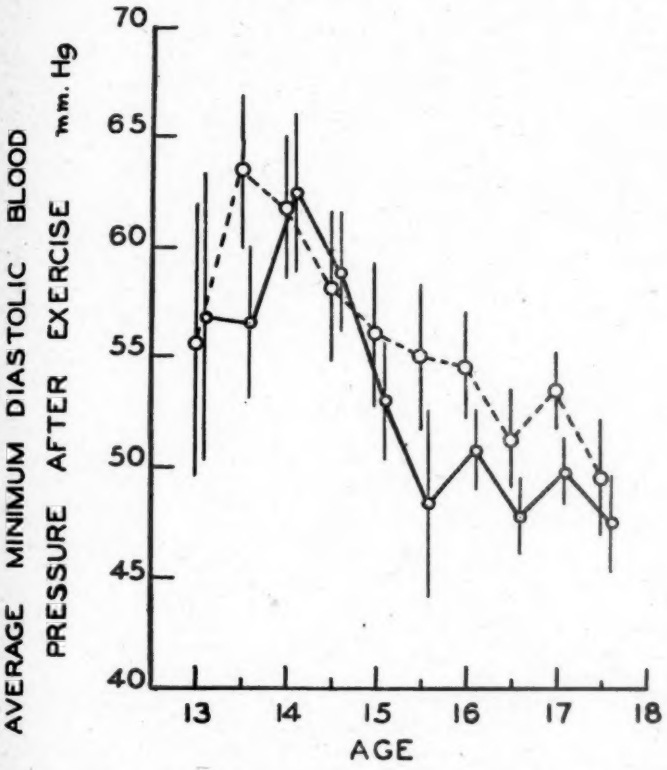

Figure 7. Average minimum diastolic blood pressure after exercise. O———O Males; O— — —O Females.

in diastolic blood pressure after exercise is greatest at age 15 and becomes less with increasing age. It is interesting to note that this is the same age at which minimal values for basal diastolic pressures were observed (7, 9). In individual cases low diastolic pressures after exercise were more closely related to physiological immaturity, as indicated by growth rate,

ossification of epiphyses, and secondary sex characters than to chronological age. The drop in diastolic blood pressure after severe exercise in adolescents has also been observed in four boys by Schneider and Crampton (6). Figure 8 shows the

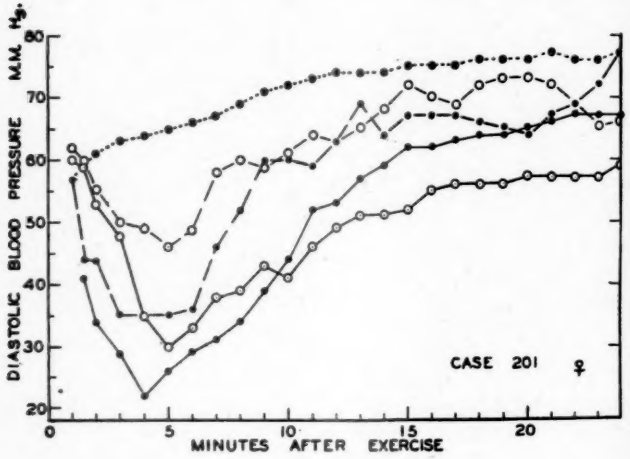

Figure 8. Age changes in diastolic blood pressure response to severe exercise. Repeated observations on same girl. Case 201. ●——●——● Age 13 yrs. 7 mo.; —●— —●— Age 13 yrs. 10 Mo.; O—O—O Age 14 yrs. 9 mo.; O—O—O Age 16 yrs. 4 mo.; ●— — —●— — —● Age 17 yrs. 4 mo. Curves show disappearance of drop in diastolic blood pressure after exercise with increasing age.

diastolic pressure response to exercise in the same subject at different ages. This figure shows that the depression in diastolic blood pressure after exercise diminished with increasing age and maturity in this subject.

In a preliminary analysis of these observations (4) it was concluded that after exercise the adult vessels relaxed less markedly than those of the children and that among the latter the boys' arteries reacted more rapidly than girls'. This conclusion was based on the implication that low diastolic pressure with raised pulse rate and pulse pressure as observed after exercise could only have been accomplished by vasodilation decreasing the perhipheral resistance faster than the cardiac output dropped. Variation in the time and intensity

relation of these two vascular responses—relaxation followed by constriction—which appear to have been present in every case, can be held to account for all the types of diastolic pressure curves obtained on the basis of the three type curves shown in the diagram of Figure 9. The dotted lines are

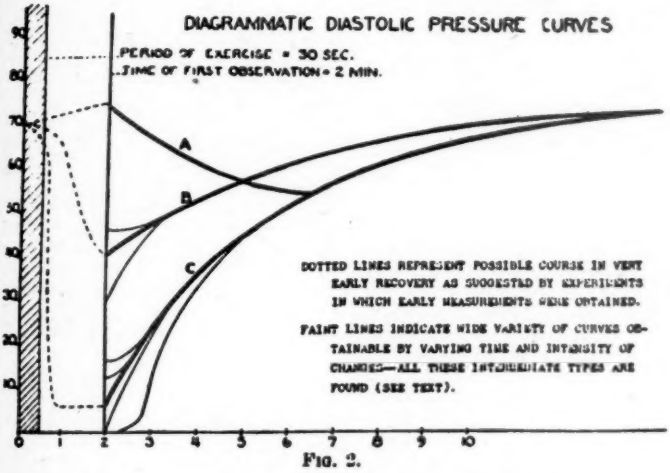

Figure 9. Diagrammatic diastolic blood pressure curves after exercise. For discussion see text. (From Proc. Soc. Exp. Biol. and Med., 33:5–8, 1935).

hypothetical and suggest possible courses of events in the interval between our resting measurements and our earliest recovery measurements. For the most part, the adults tested fell into category B and the children into A and C with a preponderance of boys in C and of girls in A. In view, however, of the notorious uncertainty of diastolic pressure measurements, the use of these conceptions in interpreting individual differences in diastolic pressure recovery curves must be reserved until more precise information is available on cardiac output in these circumstances and until the relative speed of arterial response in such subjects has been measured by other techniques.

Age changes in oxygen uptake after exercise: After exercise the oxygen uptake was markedly increased. Average values

for boys and girls at increasing chronological age are shown in Figure 10. From this figure it may be seen that at age 13,

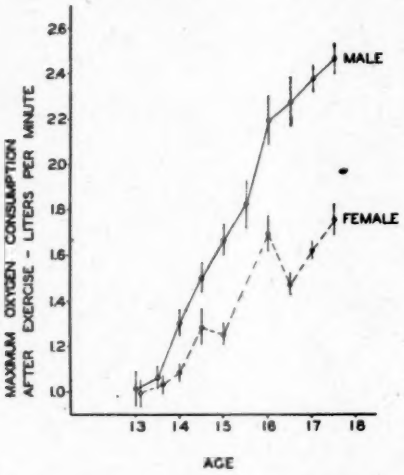

Figure 10. Age changes in metabolic response to severe exercise. Maximum oxygen uptake after exercise, liters per min. O———O Males; O— — —O Females.

the average maximum oxygen uptake was 1.0 liters per min. for both boys and girls. With increasing age, the maximum rate of oxygen uptake increased to 2.5 liters per minute in 17.5 year-old boys; in 17.5 year-old girls the average rate increased to only 1.7 liters per minute. When the results were calculated in terms of deviations from the basal oxygen consumption of each subject, the difference between the sexes disappeared. The maximum rate of oxygen uptake increased from about 500 per cent basal values at age 13 to 980 per cent of basal values at 17.5 years (Figure 11). Thus the capacity for increasing the rate of oxygen uptake increases markedly during adolescence.

Inspection of individual curves of oxygen uptake after exercise (Figures 2 and 3) indicates the rapidity with which recovery takes place. By interpolating from individual recovery curves the rate of oxygen uptake at 1 minute after

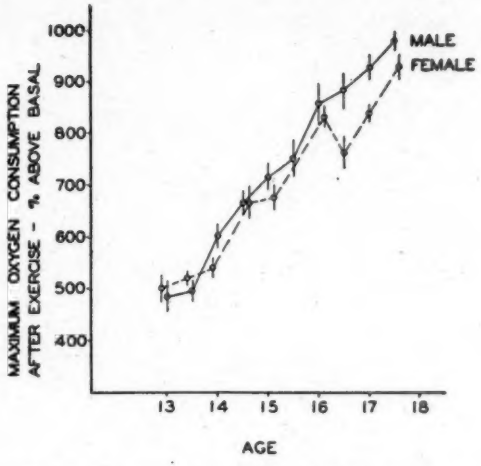

Figure 11. Age changes in metabolic response to severe exercise. Maximum oxygen uptake. Per cent of basal consumption.
O————O Males; O— — —O Females.

exercise and calculating average values in terms of per cent deviation from basal values, a rough indication of the recovery process may be obtained. Figure 12 shows the average rate of oxygen uptake 1 minute after the end of exercise for both boys and girls at increasing ages. This curve indicates that recovery is more rapid in males than females at all ages, and that recovery is less rapid in 17.5 year-old males than in 13 year-old males. Comparison of Figure 12 with Figure 11 shows that the oxygen uptake diminishes more during the first minute in older subjects than in younger subjects, since in 18-year-old boys, the average oxygen uptake falls from 980 per cent above basal levels to 460 per cent above basal within the first minute after exercise. In 13 year-old boys, the decrease during the first minute is from 500 per cent of basal values to 435 per cent. This rapid change during the first minute of recovery does not continue since evidence is offered in the following section that total recovery of oxygen uptake is slower in older children than in younger. These results provide evidence for the concept that two factors are operating

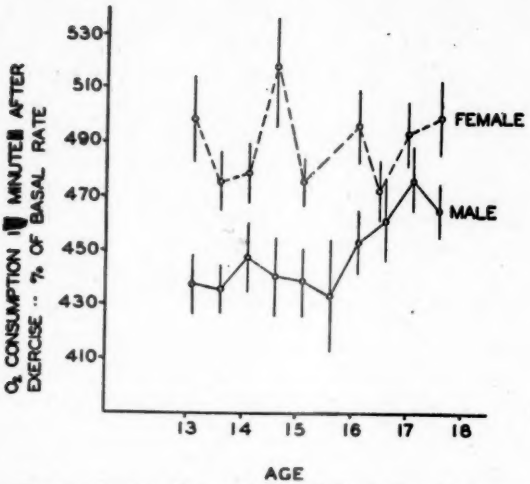

Figure 12. Age changes in metabolic response to severe exercise. Oxygen uptake one minute after end of exercise. Per cent of basal consumption.
O————O Males; O— — — —O Females.

in the fall of oxygen uptake after exercise, one of which accounts for the rapid initial fall in oxygen uptake on the cessation of exercise, the other for the remainder of recovery occurring after severe exertion (1). It is only the factors operating to produce the period of rapid fall that apparently increase in effectiveness with age. These factors are also more effective in boys than in girls.

Casual inspection of individual curves of oxygen uptake (Figures 2 and 3) showed that some of the younger adolescents returned to basal rates within 20 minutes after exercise in contrast to college students and adults who required as long as 3 hours to affect the same degree of recovery. A rough quantitative estimate of these differences could be obtained by calculating the deviation from basal of oxygen uptakes at 20, 30, or 45 minutes after exercise for each experiment. Such a procedure would, however, be based on single determinations of oxygen uptake which are less reliable than the mean of a number of determinations. Hence, it seemed wise to devise a single statistic which would be based on all the determinations

of oxygen uptake made in each experiment. It was found that by fitting the empirical equation $y=ax^{-b}+c$, in which y=oxygen uptake (cc. O_2 per kg. per min.) at time x (min. after exercise), and c=oxygen uptake at $x=\infty$ (equivalent to the basal oxygen consumption, and *a* and *b* are constants derived from the statistical analysis of the data of each experiment, such a single statistic could be derived. In this equation values of b express the relative instantaneous velocity of recovery of oxygen uptake at time x (2). Figure 13 shows

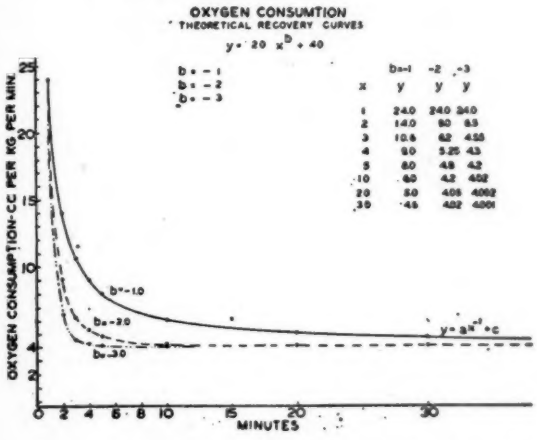

Figure 13. Theoretical recovery curves, showing effect of changing values of b in the equation $y=ax^{-b}+c$.

three theoretical curves calculated for increasing values of b. As may be seen from this figure, the higher the value of b, the more rapid the recovery and in fact, b may be used as the best available measure of the rapidity of recovery.[6] Values of b were statistically estimated for each experiment by the method previously described (2). Evidence that the value of b was a characteristic of the recuperative capacity of the

[6]As previously indicated (1, 2), a complete description of both the rapid and slow phases of recovery would require the use of an equation containing two exponentials. However, an empirical test showed that the equation with a single exponential could be used when observations taken at times less than 1 minute after exercise were disregarded. The equation used was thus effective in characterizing the slow phase of recovery.

individual and was independent of the amount of work done was provided by experiments in which the same subject performed different amounts of work on the bicycle ergometer. Values of b estimated from different experiments on the same subject are shown in Table I. From this table it is clear that

TABLE I

Values of Recovery Coefficient for Oxygen Uptake with Different Amounts of Exercise.

(values of b)

S	Age Years	Kind of Exercise	O_2 Uptake 1 min. After Exercise cc./kg./min.	b
NC	22	ergometer	16.8	—1.028
NC	22	stairs	27.3	—1.008
Fus	24	stairs	27.2	—1.036
Fus	24	stairs	18.0	—0.999
Cas	22	ergometer	19.0	—1.018
Cas	22	stairs	32.5	—1.021
Bin	16.7	stairs	57.2	—2.069
Bin	17.3	stairs	27.1	—1.744
Han	11.0	stairs	35.7	—1.676
Han	11.0	ergometer	18.2	—1.681

the value of b obtained was not systematically influenced by the amount of work done or by the degree of metabolic displacement produced. Figure 14 shows that with increasing age the average value of b diminished.

While the complete statistical analysis of the exercise data remains to be completed, this preliminary survey indicates that with increasing age there is a reduction in the slow recuperative capacities of the individual with respect to oxygen uptake after exercise.

SUMMARY

The physiological responses to severe exercise have been measured in the same group of 100 children as they progressed through adolescence and attained maturity. After measurements of pulse rate, blood pressure and oxygen uptake were made under basal conditions, each child climbed 5 flights of stairs (a height of 17.7 m.) as rapidly as possible and then

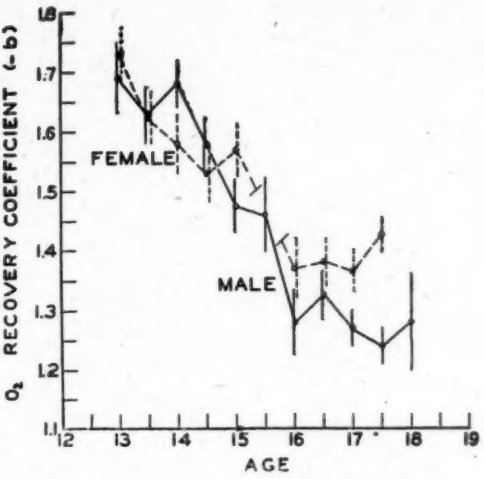

Figure 14. Age changes in rate of recovery of oxygen uptake after severe exercise. Average values for —b in the equation $y=ax^{-b}+c$, where y = oxygen uptake in cc. per kg. per min. at time t and c = basal oxygen consumption.
O————O Males; O— — — —O Females.

lay down on a cot. Continuous measurements of pulse rate, respiration rate and volume, oxygen uptake and carbon dioxide elimination were made over a 45-minute recovery period. Systolic and diastolic blood pressure measurements were made at ½–1 minute intervals. From the data collected, recovery curves were plotted for each variable for each experiment. A preliminary analysis of the data has been made to demonstrate age changes in the physiological responses and rate of recovery after this exercise. The average increase in pulse rate after exercise diminishes with increasing age. The increase in pulse rate was greater in boys than in girls at all ages. Pulse rates failed to return to basal levels within the 45 minute recovery period. The increase in systolic blood pressure after exercise was greater in boys than in girls. In girls, there was little or no change with age, but in boys, the maximum systolic blood pressure increased with age. The rise in systolic blood pressure after exercise was more rapid in

younger than in older children. A marked decrease in diastolic blood pressure after exercise was observed in young children which disappeared with increasing age. After exercise the maximum rate of oxygen uptake attained increased with increasing age. The fall in oxygen uptake during the first minute after exercise was also greater in older than in younger children. However, the rate of recovery of oxygen uptake during the later stages of recovery was slower in older than in younger children.

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Calling Attention To

Items of Possible Interest to Friends of Our Effort
May, 1946

1. American Chemical Society meeting in Atlantic City, April 8–12, offered medicinal chemistry program rivalling that of Federation of American Societies for Experimental Biology held month previously: symposia included nutritive value of protein hydrolyzates, microbiology, anti-malarials, clinical biochemistry, enzymes, metabolism of acetic acid, vitamins, premedical education, pharmacological agents, and biochemical and biophysical studies on viruses. But commercially inspired officials hush on penicillin continues.

2. Therapeutic Notes: W. W. Zuelzer and F. N. Ogden find 5 mgm. folic acid daily by mouth specific for megaloblastic macrocytic anemia (*Proc. Soc. Exp. Biol. Med.* 61:176, 1946). D. State and O. H. Wangensteen recommend procaine intravenously, 1 gm. in 500 cc. physiological saline solution, in treatment of delayed serum sickness (*J.A.M.A.* 130:990, April 13, 1946). E. A. Brown & Co. recommend 2% carbamide peroxide in 50% glycerol and water as safe and effective topical antiseptic (*New Eng. J. Med.* 234:468, April 4, 1946). B. L. Coley & Co. review bacterial toxin therapy of malignancy (*Cancer Res.* 6:205, 1946).

3. Of Cultural Interest: McGraw-Hill, 330 W. 42d, N.Y. 18, announces *Science Illustrated*, large sized jazz science monthly at $3 annually. Froben Press, 4 St. Luke's Place, N.Y. 14, offers W. Marmelszadt's *Musical Sons of Aesculapius*, illustrated at $3. J. B. Lippincott, Philadelphia 5, issues D. Guthrie's *History of Medicine*, 448 pp., illustrated, at $6. A. A. Knopf publishes A. Castiglioni's *Adventures of the Mind*, 448 pp. illustrated, at $4.50. Macmillan, 60, 5th Ave., N.Y., issues A. S. Eve's *Rutherford*, a significant biography, 451 pp., at $5. A. Kardiner's *Psychological Frontiers of Society* appears from Columbia Univ. Press, N.Y., with 475 pp., at $5.

4. Enzymes and Growth: D. Grob well discusses control of activity of proteolytic enzymes (*J. Gen. Physiol.* 29:219, 249, 1946). W. Shive & Co. study competitive analogue-metabolite growth inhibitions, and suggest product inhibition index as molar ratio of analogue to metabolite at which rate of synthesis of product is reduced enough to prevent growth of organism in medium free of product (*J. Biol. Chem.* 162:451, 463 1946). F. Schlenk & Co. note inactivation of glutamic-aspartic transaminase by sunlight and ultraviolet, not X-ray (*Proc. Soc. Exp. Biol. Med.* 61:183, 1946). Our C. E. Lankford and P. K. Skaggs report cocarboxylase as a growth factor for gonococci (*Arch. Biochem.* 9:265, 1946). P. R. Cannon & Co. demonstrate importance of protein reserves for antibody production (*J. Immunol.* 52:267, 1946).

5. Symposia and Reviews: W. B. Dublin neatly reviews knowledge of reticulum (*Arch. Path.* 41:299, 1946). L. J. A. Parr and E. Shipton offer full review of rheumatic spondylitis (*Med. J. Austral.* 1:277, March 2,

1946). Note excellent symposium on radiobiology (*Brit. Med. Bull.* 4:1–65, 1946). E. M. Hildebrand introduces general symposium on weed destruction, important in pollen and allergy control (*Science* 103:465, 469, 472, etc., April 19, 1946).

6. OTHERWISE: H. H. Anderson & Co. report physical and biological properties of subtilin (*Science* 103:419, April 5, 1946). T. F. Gallagher & Co., E. C. Kendall & Co., E. S. Wallis & Co. go to work on synthetic steroids (*J. Biol. Chem.* 162:491, 555, 633, 1946). B. E. Abreu & Co. offer neat biochemorphic study of thiophene analogues of trasentin (*J. Pharmacol.* 86:208, 1946). R. H. Goetz (Cape Town) describes rate and control of blood flow through skin of lower legs (*Amer. Heart J.* 31:146, 1946). H. S. Simms shows log increase in mortality as manifestation of aging (*J. Gerontol.* 1:13, 1946). J. Furth finds thymectomy reduces incidence of leukemia in high leukemia strain mice, probably by removing potentially malignant cells (*ibid.* p. 46). J. E. Ayre and W. A. G. Bauld report low thiamine with high estrogen is dangerous precancerous combination (*Science* 103:441, April 12, 1946). E. R. Loew & Co. give pharmacological data on benadryl (*J. Pharmacol.* 86:229, 1946). Our C. N. Frazier and E. H. Frieden discuss action of penicillin (*J.A.M.A.* 130:677, March 16, 1946). H. K. Faber & R. J. Silverberg find pharynx favorable site for primary penetration of polio virus and primary lesion in peripheral ganglia (*J. Exp. Med.* 83: 329, 1946). E. C. Dodds discusses ancient apothecaries and modern biochemists (*Lancet* 1:221, February 16, 1946).

JUNE, 1946

1. GENERAL: C. G. Hartman makes pertinent plea for support of the little researcher (*Science* 103:493, April 26, 1946). Cambridge Univ. Press offers H. Burrows' *Biological Actions of Sex Hormones* (Cambridge, 1946, $8.50). E. Hesse writes *Narcotics and Drug Addiction* (Philosophical Library, 15 E. 40th, N.Y. 16, 1946, $3.75). M. J. D. White reviews *Animal Crytology and Evolution* (Macmillan, 60 5th Ave., N.Y. 11, 375 pp. 1946, $7.50). Artistic report on U. S. Army medicine is compiled by D. Mackenzie (Blakiston, Philadelphia, 470 pp., 1946, entitled *Men Without Arms*, $5). L. Whitby also claims that scientists are artists (*The Science and Art of Medicine*, Macmillan, N.Y. 11, 1946, $0.50). A. B. Hastings and M. B. Shimkin report on medical research misson to Soviet Union (*Science*, 103: 605, May 17, 1946). S. Epstein and B. Williams rhapsodize on *Miracles from Microbes: The Road to Streptomycin* (Rutgers Univ. Press, New Brunswick, N. J., 1946, $2). H. E. Sigerist collects provocative essays, mostly on medical education, under title *The University at the Crossroads* (Schuman, 20 E. 70, N.Y., 1946, $2.75). C. P. McCord writes well on maladies of workers under title *A Blind Hog's Acorns* (Cloud, Chicago, 1945, 311 pp., $3). S. Hook goes after M. Adler in writing sensibly on *Education for Modern Man* (Dial, N. Y., 227 pp., $2.75, 1946). For powerful poetry, note H. Hagedorn's *The Bomb That Fell on America* (Santa Barbara, Pacific Coast Publ., 57 pp., 1946, $1.25). D. Carter bravely tackles social problems in *Sin and Science* (Heck-Cattell, 33 W. 42, N.Y. 18, 1946, $2.50). B. J. Stern discusses *Medicine in Industry* (Commonwealth,

N.Y., 1946, 209 pp., $1.50). J. Ortega y Gasset (Madrid) is brilliant and bewildering in *Concord and Liberty* (Norton, 70 5th, N.Y. 11, 1946, $3).

2. Nervous System Enzymes: F. M. Forster & Co. show similarity of acetylcholine treated sensory cortex and epileptic cortex (*J. Neuropath. and Exp. Neurol.* 5:24, 1946). W. Feldberg and T. Mann find adenosine triphosplate, citric acid, and unknown dialyzable activator increase enzymic synthesis of acetylcholine in brain and nervous tissue (*J. Physiol.* 104:411, 1946). F. Crescitelli & Co. show by di-isopropyl fluorphosphate that nerves can conduct in absence of cholinesterase, but Th. Bullock & Co. interpret similar experiments as showing release and removal of acetylcholine essential for conduction (*J. Neurophysiol.* 9:241, 253, 1946). D. Nachmansohn & Co. offer much evidence for acetylcholine formation in nerve axon and show its relation to conduction (*J. Biol. Chem.* 163:475, 1946).

3. Pharmacological Notes: A. N. Bose & Co. find toxicity of urea stibamine and other antimonials may be reduced by removing antimonious acid (*Indian Med. Gaz.* 81:13, 1946). J. E. P. Toman & Co. describe rapid method of appraising antiepileptics and find diphenyl hydantoia and phenobarbital show highest protective index, with tridione equalling phenobarbital (*J. Neurophysiol.* 9:230, 1946). F. Dickens reports on toxic effects of ozygen on brain metabolism and tissue enzymes (*Biochem. J.* 40:145, 171, 1946). B. P. Babkin & Co. (*Rev. Canad. Biol.* 5:72, 1946) confirm E. Starkenstein (*Med. Klin.* 23:1437, 1927) that scopolamine, or small doses of bulbocapnine with NaBr, help control motion sickness. W. Jacobson and D. M. Simpson offer evidence that leucopterin or related purine complexes are the effective antipernicious anemia factors (*Biochem. J.* 40:3, 9, 1946). H. C. S. Aron & Co. report that fever temperatures reduce plasma vitamin A and carotene (*Proc. Soc. Exp. Biol. Med.* 61:271, 1946). C. J. D. Zaragonetis & Co. note immunity following p-amino benzoic acid therapy in scrub typhus (*ibd.* p. 240). J. M. Rogoff & Co. discuss nervous system mechanism for adrenin secretion (*ibid.* p. 251). P. De reports blood sugar levels vary directly with depth of anesthesia, depending on release of hypothalamic sympathetic center from cortical control (*Indian Med. Gaz.* 81:17, 1946). Our G. R. Herrmann finds that choline helps to mobilize and metabolize cholesterol from blood and tissues (*Proc. Soc. Exp. Biol. Med.* 61:302, 1946).

4. Etc.: Oleanders to B. J. Anson for skilled editing of *Quart. Bull. Northwestern Med. School:* in current issue note H. B. Bull's chemical note on elastic elements of skeletal muscle, H. W. Magoun's review of extrapyramidal system, L. Doyle's appreciation of A. I. Kendall, E. W. Hagens' article on otosclerosis, and E. H. Vincent's note on doctors and music (20:175, 180, 192, 215, 240, 1946). J. P. Chu & Co. discuss relation between uterus and corpus luteum (*J. Endocrinol.* 4:392, 1946). A. C. Bottomley exhaustively treats of logistic dose-response curves in assays measured by growth of test organ (*ibid.* p. 399). D. G. Sharp & Co. present fine shadowed electron micrographs of viruses (*Proc. Soc. Exp. Biol. Med.* 61:259, 1946). G. H. Hyslop and C. E. Dunlap review effects of electrical and radiation injury (*Occup. Med.* 1:199, 237, 1946).

JULY, 1946

1. LIGHT SUMMER READING: With undue fanfare appears A. A. Bogomolets' *The Prolongation of Life* (Duell, Sloan & Pearce, N.Y., 1946, $1.50). H. Cramer reviews *Mathematical Methods of Statistics* (Princeton, 1946, 570 pp., $6). Commonwealth Fund issues Studies of N.Y. Academy of Medicine Committee on Medicine and the Changing Order, including B. J. Stern's *Medical Services by Government-Local, State and Federal* (N.Y., 1946, 226 pp., $1.50). D. M. Matthews discusses *The Surgery of Repair: Injuries and Burns* (C. C. Thomas, Springfield, Ill., 1946, 400 pp., $10). E. Urbach offers *Skin Diseases, Nutrition and Metabolism* (Grune & Stratton, N.Y., 1946, 750 pp., $10). L. G. Lowry's *Psychiatry for Social Workers* is well suited, bibliography and all, for medical students and general practitioners (Columbia Univ. Press, N.Y., 1946, 337, $3.50). Mrs. M. L. Duran-Reynals dekruifs over *The Fever Bark Tree: The Pageant of Quinine* (Blakiston, Philadelphia, 1946, $2.80). J. S. Lawrence neatly summarizes *The Sulphonamides in Theory and Practice* (H. K. Lewis, London, 1946, 125 pp., 9s). E. T. Engle edits Proceedings of Fertility Conference: *Diagnosis in Sterility* (C. C. Thomas, Springfield, Ill., 1946, 237 pp., $5). C. E. ZoBell monographs wisely on *Marine Microbiology* (Chronica Botanica, Waltham, Mass., 1946, 255 pp., $5). L. J. Soffer well reviews *Diseases of the Adrenals* (Lea & Febiger, Philadelphia, 1946, 304 pp., $5.50). L. Thorndike laboriously edits *The Herbal of Rufinus* (Univ. Chicago Press, 1946, 476 pp., $5). L. Dexter translates, revises E. Braun-Mendndez & Co., *Renal Hypertension* (C. C. Thomas, Springfield, Ill., 1946, 493 pp., $6.50). E. T. Bell surveys *Renal Diseases* (Lea & Febiger, Philadelphia, 1946, 434 pp., $7). E. E. Robinson offers provocative essays in *The New United States* (Stanford Press, 1946, 141 pp., $2.50). Then M. J. Ward conjures up *The Snake Pit*, with shock therapy (Random House, N.Y., 278 pp., $2.75).

2. SYMPOSIA AND REVIEWS: Note excellent symposium on diabetes, with C. H. Best on fat transport, H. O. Mosenthal on blood sugar tests, J. P. Peters on use of carbohydrates, and I. A. Mirsky on etiology (*Am. J. Digest Dis.* 13: 127–170, May, 1946). A. O. Whipple, G. J. Heuer & Co. contribute to symposium on cholecystitis (*Bull. N.Y. Acad. Med.* 22:281–319, 1946). C. A. Doan well reviews panmarrow hematopoiesis and splenic hematopenia in Kretschmer Lecture (*Proc. Inst. Med. Chicago* 16:178, 1946). Timely is C. M. Child's review of organizers in development and the organizer concept (*Physiol. Zool.* 19:89–148, 1946). K. H. Beyer reviews biochemorphology of sympathomimetic amines (*Physiol. Rev.* 2:169, 1946). H. G. Wood summarizes hot stuff on carbon dioxide fixation and tricarboxylic acid cycle (*ibid.* p. 198). F. A. Fuhrman collects data on effect of body temperature on drug action (*ibid.* p. 247). S. J. Thannhauser and G. Schmidt review lipins and lipidoses (*ibid.* p. 275). R. St. A. Heathcote offers full review on pharmacology and therapeutic uses of diamidines (*J. Trop. Med. Hyg.* 49:8, 33, 1946).

3. CANCER: H. B. Andrevont appropriately gives 1st E. A. Allen Lecture on the mammary tumor agent and its implications in cancer research (*Yale*

J. Biol. Med. 18:333, 1946). R. G. Green & Co. report that the milk agent of mouse mammary cancer dies out on serial transmission (*Proc. Soc. Exp. Biol. Med.* 61:362, 1946). E. L. Howes well discusses regeneration patterns in skin injury from carcinogens and finds no evidence for direct stimulation to tumor formation (*Cancer Res.* 6:298, 1946). E. Boyland shows tumor inhibition by diamino diphenyl ethers and sulfamino quinolines (*Biochem. J.* 40:55, 1946).

4. And Also: R. and H. Croxatto (Santiago, Chile) find hypertensinase activity of plasma related to aminopeptidase (*Proc. Soc. Exp. Biol. Med.* 61:330, 1946). D. Scherf claims control of anginal attacks due to rheumatic valvular lesions with thiouracil (*Rev. Argentina Cardiol.* 12: 201, 1945). H. Becks, M. E. Simpson, and H. M. Evans continue studies on skeletal changes after hypophysectomy (*Anat. Rec.* 92:109, 1945) by noting dentin thickening at expense of pulp (*Arch. Path.* 41:457, 1946). A. S. Wiener & Co. report that detailed studies on inheritance of the 8 Rh blood types confirm theory of 6 chief allelic genes, and that Hr factor increases chance of accurate exclusion in disputed paternity (*Proc. Soc. Exp. Biol. Med.* 61:382, 1946—note his remarks on pathogenesis of erythroblastosis (*ibid.* p. 390). E. L. Keeney recommends 10 per cent sodium caprylate ointment or 20 per cent aqueous solution for local application in moniliasis (candidosis) of skin or mucous membranes (*Bull. Johns Hopkins Hosp.* 78:333, 1946). A. Brown and A. L. Goodall find average diurnal variation in hemoglobin in healthy humans in bed to range from 0.54 gm. per 100 cc. to 0.93 (*J. Physiol.* 104:423, 1946). Our M. Fulton and S. F. Curtis contribute to the taxonomy of Rettger's and related bacteria (*Proc. Soc. Exp. Biol. Med.* 61:334, 1946). R. N. McCulloch recommends dibutyl phthalate as an effective insect repellant in control of scrub typhus (*Med. J. Austral.* 1:717, May 25, 1946).

August, 1946

1. Anesthesia: H. Schuman announces forthcoming publication of V. Robinson's *History of Surgical Anesthesia* as part of centenary effort. American Society of Anesthesiologists announces Morton Centennial Celebration, Hotel Sheraton, Boston, October 15, 16 and 17, with obvious program. English offer excellent symposium on anesthesia, celebrating the centenary (*Brit. Med. Bull.* 4: 81–155, '46) with experimental notes on local anesthetics and blood pressure by J. H. Burn on morphine substitutes by E. C. Dodds, on atropine substitutes by H. R. Ing; clinical notes on trichlorethylene and curare by C. L. Hewer, and historical notes, with British bias by B. M. Duncum, G. S. W. Organe and A. C. King. C. C. Scott and K. K. Chen confirm high analgesic power of new diphenyl butanone compds. (*J. Pharmacol. Exp. Therap.* 87: 63, '46). J. Stalport offers review of medicated aerosols (*Arch. Internat. Pharmaco.* 71: 248, '45). S. Krop notes local anesthetic action of pyridium (*Anesth. & Analg.* 25: 110, '46). R. K. Richars and K. E. Kueter report on competitive drug effects referring to PABA and procaine convulsions (*J. Pharmacol. Exp.*

Therap. 87: 42, '46). S. E. Sulkin & Co. suggest general anesthesia in therapy or neurotropic virus infections (*Science* 104: 53, July 19, 1946).

2. BIOCHEMORPHOLOGY: Biochemorphic character of war research in pharmacology well shown by recent reports: A. Gilman on therapeutic applications of chemical warfare agents, including 2, 3-dimercaptopropanol (BAL, British Anti-Lewisite) for heavy metal poisoning, Di-isopropyl fluorophosphate (DFP) as an anticholinesterase, of possible use in myasthenia gravis and glaucoma, and nitrogen mustards as anti tumor agents (*Fed. Proc.* 5: 285, '46); F. S. Philips on insecticides and rodenticides, including DDT, hexachlorcyclohexane ("666"), dimethyl phthalate, alphanaphthyl thiourea (ANTU) and Na fluoroacetate (*Ibid.* p. 292); E. K. Marshall on chemotherapy of malaria, including the 8-amino quinolines, such as SN 13, 276 (8-5-isopropylamino-anylamino-6-methoxy-quinoline) which is highly curative with low toxicity, and H. Molitor on bacterial chemotherapy (*Ibid.* 298, 304). W. H. Powers edits Vol. II of Wayne lecture series on Advancing Fronts in Chemistry, entitled *Chemotherapy*, with articles on chemotherapy of Tb by W. H. Feldman, on synthetic antispasmodics by F. F. Blicke, on sulfa drugs by E. H. Northey, on antimalarials by H. S. Mosher, on organometallic chemotherapeutic agents by C. K. Banks, and on chemotherapy of parasitic diseases by W. H. Wright (Reinhold, 330 " 42, NY, 156 pp., $3.25, 1946). R. B. Angier and large Co synthesize liver L. casei hematopoietic factor as pteroylglutamic acid (*Science* 103: 667, May 31/46). S. Friedlaender & Co. find pyribenzamine better antihistaminic cmpd. than benadryl (*Proc. Soc. Exp. Biol. Med.* 62: 65, '46). T. D. Spies & Co. report on antipernicious anemia effects of thymine, which is 5-methyl uracil, so why not get after other alkyl derivatives? (*J. Lab. Clin. Med.* 31: 643/46; *Blood* 1: 185/46).

3. BOOKS: Tough going but worth it is F. S. C. Northrop's *Meeting of East and West: An Inquiry Concerning World Understanding* (Macmillan, NY, '46, 531 pp., $6). Helpful and stimulating is D. E. Green's *Currents in Biochemical Research* with chapters by 31 leaders (Interscience Publ., NY 3, '46, 500 pp., $5). J. R. Neuman and B. Russell newly edit K. Pearson's edition of W. K. Clifford's *The Common Sense of the Exact Sciences*, first published in 1885 (Knopf, NY 22, '46, $4) R. G. Hoskins offers *The Biology of Schizopherenia* (Norton, NY 11, '46, $2.75). H. F. Brandt discusses *The Psychology of Seeing* (Philosophical Lib., NY16, '46, $3.75). L. Meriam gives pertinent analysis of Relief & Social Security (Brookings Inst., Washington, '46, $5). H. Haymaker and B. Woodhall issue well illustrated *Peripheral Nerve Injuries* (Saunders, Phila., '46, 227 pp., $4.50). S. Soskin and R. Levine offer *Carbohydrate Metabolism: Correlation of Physiological, Biochemical & Clinical Aspects* (Univ. Chicago Press, '46, 315 pp. $6).

4. NOTEWORTHY: G. Roskin (Moscow) discusses toxin therapy of experimental cancer, referring to influence of protozoan infections, e.g., trypanosoma cruzei, on cancer (*Cancer Res.* 6: 363/46). E. Asmussen and O. Boje show that high temperature in working organism facilitates

the performance of work (*Acta Physiol. Scand.* 10: 1, '45, now almost entirely in English). W. C. Alvarez discourses on cerebral arteriosclerosis with small unrecognized apoplexies (*Geriatrics* 1: 189/46). P. B. Prince and T. F. Lee report interesting experiments on gastric digestion of living tissue (*SGO* 83: 61/46). R. H. Silber and I. Clark show that withholding food after oral administration of sulfa drugs increases blood concentration by decreasing fecal loss (*Arch. Biochem.* 10: 9/46). E. A. Fennel & Co. describe effects of penicillin on bacterial morphology (Hawaii Med. J. 5: 257, 259/46). H. B. Stein doubts value of erythrocyte sedimentation rate as diagnostic aid in jaundice (*S. Afr. J. Med. Sci.* 11: 34/46). Our J. D. Weaver discusses psychotherapeutic effects of estrogenic hormones (*South. Med. J.* 39: 581/46). Our M. Pollard & Co. continue experiments on Bullis fever (*Am. J. Trop. Med.* 26: 175/46).